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PART II

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

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BACTERIAL VACCINES AND BACTERIAL ANTIGENS WITH NO U.S. STANDARD OF POTENCY

Implementation of Efficacy Review

[4110-03]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Parts 601 and 610]

[Docket No. 77N-0091]

BACTERIAL VACCINES AND BACTERIAL ANTIGENS WITH NO U.S. STANDARD OF POTENCY

Implementation of Efficacy Review

AGENCY: Food and Drug Administration.

ACTION: Proposal.

SUMMARY: This is a proposal to amend the biologics regulations in response to the report of the Advisory Review Panel on the safety, effectiveness, and labeling of bacterial vaccines and bacterial antigens that have "No U.S. Standard of Potency." In addition, on the basis of the Panel's findings and recommendations, the Commissioner of Food and Drugs is announcing his conclusion that none of these products is in Category I (safe, effective and not misbranded) and that certain products are in Category IIIA (on the market during further studies in support of effectiveness) and is inviting comments and the submission of views and additional data on the classification of these products. The Commissioner is also announcing his conclusion of those products in Category II (unsafe, ineffective or misbranded) and in Category IIIB (off the market pending completion of studies to determine effectiveness). On or before December 8, 1977, the Commissioner will publish a notice of opportunity for hearing on his intention to revoke the licenses for these products.

DATES: Written comments by January 9, 1978.

ADDRESS: Written comments to Hearing Clerk (HFC-20), Food and Drug Administration, Room 4-65, 5600 Fishers Lane, Rockville, Md. 20857.

FOR FURTHER INFORMATION CONTACT:

John J. Singleton, Bureau of Biologics (HFB-620), Food and Drug Administration, Department of Health, Education, and Welfare, 6110 Executive Blvd., Rockville, Md. 20857 (301-443-1920).

SUPPLEMENTARY INFORMATION: In the FEDERAL REGISTER of February 13, 1973 (38 FR 4319), the Commissioner issued § 273.245 (21 CFR 273.245 subsequently recodified as § 601.25 in the FEDERAL REGISTER of November 20, 1973 (38 FR 32048)) concerning procedures for review of safety, effectiveness, and labeling of biological products licensed prior to July 1, 1972. The biologics to be reviewed were assigned, pursuant to a redesignation of panel assignments published in the FEDERAL REGISTER of June 19, 1974 (39 FR 21176), to one of the following categories: (1) Bacterial Vaccines and Bacterial Antigens with "No U.S. Standard of Potency," (2) Bacterial Vaccines and Toxoids with Standards of Potency, (3) Viral Vaccines and Rickettsial Vaccines, (4) Allergenic Extracts, (5) Skin Test Antigens and (6) Blood and Blood Derivatives.

Pursuant to § 601.25, the Commissioner assigned responsibility for the initial review for each of the products in these categories to a separate independent advisory panel consisting of qualified experts. The Commissioner charged each Panel to: (1) evaluate the safety and effectiveness of the biological product, (2) review the labeling of the biological product, and (3) advise him on which biological products under review are safe, effective, and not misbranded, in the form of an advisory review panel report to the Commissioner. The advisory review panel was directed to include in its report a statement classifying products into one of three categories.

Category I designates those biological products determined by the Panel to be safe, effective, and not misbranded. The Panel statement may include any condition relating to active components, labeling, tests required prior to release of batches, product standards, or other conditions necessary or appropriate for their safety and effectiveness.

Category II designates those biological products determined by the Panel to be unsafe or ineffective or to be misbranded.

Category III designates those biological products determined by the Panel not to fall within either Category I or II on the basis of the Panel's conclusion that the available data are insufficient to classify such biological products, and for which further testing is therefore required. Those biological products in Category III for which continued licensing, manufacturing, and marketing are recommended are designated as Category IIIA. Those biological products in Category III for which revocation of the license is recommended (and thus continued manufacturing and marketing are denied) are designated as Category IIIB. The recommendation for either Category IIIA or IIIB is based on an assessment of the present evidence of safety and effectiveness of the product and the potential benefits and risks likely to result from the continued use of the product for a limited period of time while the questions raised concerning the product are being resolved by further study.

To facilitate review of safety, effectiveness, and labeling of these products and to provide all interested persons an opportunity to present, for consideration by the Panel, the best information available to support the stated claims for Bacterial Vaccines and Bacterial Antigens with "No U.S. Standard of Potency," the Commissioner solicited, in the FEDERAL REGISTER of August 18, 1972 (37 FR 16690), submission of data pertinent of these products.

The Commissioner particularly notes that some concern has been expressed that information submitted to FDA pursuant to § 601.25 will become public information. Data and information submitted pursuant to the August 1972 notice and falling within the provisions of 18 U.S.C. 1905, 5 U.S.C. 552(b), or 21 U.S.C. 331(j) have been handled as confidential. However, with publication of this proposed implementation and the full report of the Panel, such data and information will, pursuant to § 601.25(b)(2), be made publicly available December 7, 1977, and may be viewed at the office of the Hearing Clerk, except to the extent that the person submitting the data and information demonstrates that it still falls within one or more of the confidentiality provisions. Accordingly, comments concerning confidentiality should be submitted by December 7, 1977.

In addition, during 1972, the Commissioner issued letters to approximately 35 medical and scientific associations and consumer group organizations requesting that interested persons nominate qualified experts to serve on the Advisory Panel on Bacterial Vaccines and Bacterial Antigens with "No U.S. Standard of Potency."

The Commissioner appointed the following Panel to review the data and information submitted, and to prepare a report on the safety, effectiveness, and labeling of Bacterial Vaccines and Bacterial Antigens with "No U.S. Standard of Potency":

Panel Chairman, Richard S. Farr, M.D., Director, Department of Medicine, National Jewish Hospital and Research Center, Professor of Medicine, University of Colorado Medical Center, Denver, Colo.

Randolph M. Chase, Jr., M.D., Associate Professor (Immunology), Department of Medicine, New York University School of Medicine, New York, N.Y.

Susan Coons Dees, M.D., Professor of Pediatrics (Allergy), Duke University School of Medicine, Durham, N.C.

Harry A. Feldman, M.D., Professor and Chairman (Infectious Diseases, Epidemiology), Department of Preventive Medicine, State University of New York, Upstate Medical Center, Syracuse, N.Y.

Carolyn Coker Huntly, M.D., Professor of Pediatrics, Bowman Gray School of Medicine, Winston-Salem, N.C.

Peter E. Isaacson, M.D., Professor and Department Head (Epidemiology), Department of Preventive Medicine and Environmental Health, University of Iowa, Iowa City, Iowa.

Paul P. Van Arsdel, Jr., M.D., Professor of Medicine, Head, Division of Allergy, School of Medicine, University of Washington, Seattle, Wash.

Dr. Huntley resigned on August 7, 1973, and subsequently was replaced by: Sidney Friedlaender, M.D., (Private practice), Clinical Professor of Medicine, Wayne State University College of Medicine, Southfield, Mich.

The Panel was first convened on February 15, 1973, in an organizational meeting. Working meetings were held on: February 16, March 16-17, May 18-19, June 21-22, July 27-28, September 14-15, November 1-3, December 19-20, 1973; January 16-17, February 21-22, March 29-30, May 10-11, June 21-22, September 27-28, November 1-2, 1974; January 24-25, March 10-11, May 2-3, June 27-28, 1975; and January 29-30, 1976.

Two nonvoting liaison representatives served on the Panel. James Turner, J.D.,

nominated by the Consumer Federation of America, served as the consumer representative. John Adams, Ph. D., of the Pharmaceutical Manufacturers Association, nominated by a number of producers with products under review by the Panel, served as the industry representative. Arthur Koch, Alice Shabecoff, and Cathy Sulzberger served as substitutes for Mr. Turner during his absences. Karl Bambach, Ph. D., and Charles B. Cleveland substituted for Dr. Adams during his absences. Morris Schaeffer, M.D., Ph. D., participated in the Panel meetings in his capacity as Director of the Office of Efficacy Review, Bureau of Biologics, Food and Drug Administration. Jack Gertzog, Deputy Director, Office of Efficacy Review, Bureau of Biologics, Food and Drug Administration, served as Executive Secretary of the Panel.

Paul Sheehe, D.Sc., was selected by the Panel as its consultant in biostatistical matters.

The following individuals appeared before the Panel to express their view either at their own or the Panel's request:

Harold Baer, Ph. D.
Solomon Barr, M.D.
Robert J. Becker, M.D.
Edward Buescher, M.D.
Samuel J. DeCourcy, Jr., D.Sc.
Thomas Espersen, Esq.
Eugene N. Fox, Ph. D.
Herman Friedman, Ph. D.
George Galasso, Ph. D.
Marvin P. Goff, D.V.M.
Winfield S. Hammond, M.S.
Carolyn Hardegree, M.D.
Douglas J. Hennessy, Ph. D.
James C. Hill, Ph. D.
Julia R. Hoffmann
Peter Hutt, Esq.
Charles R. Manclark, Ph. D.
Francis Martini
Harry L. Mueller, M.D.
Jack Pavuk
Robert J. Price, D.V.M.
John Robbins, M.D.
Billie Rutt
Michael W. Rytel, M.D.
James W. Smith, Ph. D.
Gene H. Stollerman, M.D.
L. O. Tippett
J. W. Townsend, M.D.
Sheldon Wolff, M.D.

No person who so requested was denied an opportunity to appear before the Panel.

The following firms submitted data and information relating to the indicated products:

TABLE 1.—*Products reviewed, their components and license years*

Manufacturer	Product	Advisory Panel product description	Year licensed [2]	Names of components as licensed
Center Laboratories, Inc.	Allergenic Extracts of Mixed Respiratory Bacteria.	*Staphylococcus aureus* and *Albus*.	1950	Allergenic extract.
		Streptococcus milis and *salivarius*.		
		Streptococcus pyogenes, Group A.		
		D. pneumoniae, I, II, and III.		
		K. pneumoniae, two strains.		
		N. catarrhalis.		
Delmont Laboratories, Inc.	Staphage Lysate (SPL) [1], Type I.	*Staphylococcus aureus*, Type I, lysed by polyvalent phage.	1950	Bacterial antigen made from staphylococcus.
	Staphage Lysate (SPL) [1], Types I and III.	Mixture of Types I and III.	1950	Do.
Lilly and Co.	Combined Vaccine No. 4 with Catarrhalis (V-151).	Heat-killed:		Bacterial vaccines made from:
		N. catarrhalis (1915)		1. *Micrococcus catarrhalis*.
		K. pneumoniae (1915)		2. Friedlander bacillus.
		D. pneumoniae (1915)		3. Pneumococcus.
		Streptococci (1915)		4. Streptococcus.
		Staphylococci (1915)		5. *Staphylococcus albus*.
				6. *Staphylococcus aureus*.
	Mixed Vaccine No. 4 with *H. influenzae* (V-306).	Heat-killed:		Bacterial vaccines made from:
		H. influenzae (1915)		Influenzae bacillus.
		N. catarrhalis (1915)		*Micrococcus catarrhalis*.
		Streptococci (1915)		Streptococcus.
		K. pneumoniae (1915)		Friedlander bacillus.
		Staphylococci (1915)		*Staphylococcus albus*.
		Pneumococci (1915)		*Staphylococcus aureus*.
				Pneumococcus.
	Respiratory UBA (UBA-32).	Undenatured bacterial antigens of:		Bacterial antigens made from:
		Pneumococci (1931)		1. Pneumococcus.
		Streptococci (1931)		2. Streptococcus.
		H. influenzae (1939)		3. Influenza bacillus.
		N. catarrhalis (1939)		4. *Micrococcus catarrhalis*.
		Staph. aureus and *albus* (1930)		5. *Staphylococcus albus*.
				6. *Staphylococcus aureus*.
	Staphylococcus-Streptococcus UBA (UBA-48).	Undenatured bacterial antigens of: Staphylococci and streptococci.	1915	Bacterial antigens made from:
				1. *Staphylococcus albus*.
				2. *Staphylococcus aureus*.
				3. Streptococcus.
	Staphylococcus Vaccine (V-563).	Heat-killed: *Staphylococcus aureus* and *epidermidis*.	1915	Bacterial vaccine made from:
				1. *Staphylococcus albus*.
				2. *Staphylococcus aureus*.
	Streptococcus Vaccine (Intravenous) (V-677).	Heat-killed: Streptococci (Clawson and Weatherby).	1952	Streptococcus vaccine.
	Typhoid H Antigen (V-763).	Flagellar typhoid baccilli antigens.	1931	Bacterial vaccine made from typhoid baccilli.
	Entoral (V-404 and V-406).	Contains killed:		Bacterial vaccines made from:
		Pneumococci (1915)		1. Pneumococcus.
		Streptococci (1915)		2. Streptococcus.
		H. influenzae (1915)		3. Influenza bacillus.
		N. catarrhalis (1915)		4. *Micrococcus catarrhalis*.

Footnotes at end of table.

Manufacturer	Product	Advisory Panel product description	Year licensed [1]	Names of components as licensed
Hoffmann Laboratories, Inc.	Staphylococcal BAC [2]	Acellular BAC antigens from *Staphylococcus albus* and *aureus*.	1956	Bacterial antigens made from staphylococcus species.
	Pooled Skin BAC [2]	Acellular BAC from: *Staphylococcus albus* and *aureus* and *P. vulgaris*.	1956	Bacterial antigens made from: 1. Staphylococcus. 2. *Proteus vulgaris*.
	Respiratory BAC [2]	Acellular BAC from:	1956	Bacterial antigens made from:
		Strep. pyogenes, faecalis and *viridans*.		1. Streptococcus species.
		D. pneumoniae		2. *Diplococcus pneumoniae*.
		Staph. albus and *aureus*		3. Staphylococcus species.
		E. coli		4. *Escherichia coli*.
		N. catarrhalis		5. *Neisseria catarrhalis*.
		H. influenzae		6. *Haemophilus influenzae*.
	Gram-Negative BAC [2].	Acellular BAC from:	1956	Bacterial antigens made from:
		Ps. aeruginosa		1. *Pseudomonas aeruginosa*.
		E. coli		2. *Escherichia coli*.
		A. aerogenes		3. *Aerobacter aerogenes*.
	Pooled Stock BAC [2], No. 1.	Acellular BAC from:	1956	Bacterial antigens made from:
		D. pneumoniae, I, II, V, VII, and XIV.		1. *Diplococcis pneumoniae*.
		Strep. pyogenes, Grp. A, Types 3, 10, 12, and Granger.		2. Streptococcus species.
		Strep. viridans (R 1551, R 1822 and R 353).		
		Staph. albus and *aureus*		3. Staphylococcus species.
		N. catarrhalis		4. *Neisseria catarrhalis*.
		E. coli		5. *Escherichia coli*.
		H. influenzae, types a and b.		6. *Haemophilus influenzae*.
	Pooled Stock BAC [2], No. 2.	Acellular BAC from:	1956	Bacterial antigens made from:
		D. pneumoniae, III, VI, XIX.		1. *Diplococcus pneumoniae*.
		K. pneumoniae, A		2. *Klebsiella pneumoniae*.
		Strep. pyogenes, 14, 18, 19		3. Streptococcus species.
		P. aeruginosa		4. *Pseudomonas aeruginosa*.
		E. coli		5. *Escherichia coli*.
		A. aerogenes		6. *Aerobactor aerogenes*.
Hollister-Stier, Division of Cutter Laboratories.	Mixed Respiratory Vaccine (MRV).	Killed bacteria:		Bacteria vaccines made from:
		Streptococci (*pyogenes, viridans* and nonhemolytic).	(1928)	1. *Strepococcus viridans*. 2. Streptococcus nonhemolytic. 3. *Streptococcus pyogenes*.
		Staph. aureus (*albus*)	(1928)	4. *Staphylococcus aureus*.
		D. pneumoniae	(1928)	5. *Staphylococcus albus*.
		N. catarrhalis	(1953)	6. *Neisseria catarrhalis*.
		K. pneumoniae	(1928)	7. *Klebsiella pneumoniae*.
				8. *Diplococcus pneumoniae*.
		H. influenzae	(1928)	9. *Haemophilus influenzae*.
	Bacterial Vaccine T-50.	Killed bacteria made to prescription.	(1928)	Bacterial vaccine made from *Streptococcus pyogenes*.
	Bacterial Vaccine, Diagnostic/Therapeutic.	Killed bacteria:		All licensed bacterial vaccines with no U.S. standard of potency and those bacterial products licensed under the general allergenic extract license.
		A. aerogenes	(1955)	
		C. pseudodiphtheriticum		
		D. pneumoniae, mixed		
		E. coli		
		G. tetragena	(1955)	
		H. influenzae	(1928)	
		H. pertussis		
		K. pneumoniae		
		N. catarrhalis	(1928)	
		P. vulgaris	(1955)	
		P. aeruginosa	(1955)	
		S. enteritidis	(1955)	
		S. paratyphi	(1955)	
		S. schottmuelleri	(1955)	
		S. typhosa	(1955)	
		S. dysenteriae	(1955)	
		S. flexneri		
		Staph. albus and *aureus*	(1928)	
		Strep. fecalis, pyogenes, viridans and *nonhemolyticus*.	(*)	
Instituto Sieroterapico Vaccinogeno Toscano "Sclavo."	Staphylococcus Toxoid "Sclavo."	*Staphylococcus aureus*	1960	Staphylococcus toxoid.
Lederle Laboratories Div., American Cyanamid Co.	Staphylococcus Toxoid:		1933	
	(Digest Modified)	*Staph. aureus* (1 strain)		Staphylococcus toxoid:
	(Formalinized)	*Staph. aureus* (3 strains)		

Manufacturer	Product	Advisory Panel product description	Year licensed [2]	Names of components as licensed
Parke, Davis and Co.	Immunovac Oral Vaccine.	Killed bacteria:		Bacterial vaccines made from:
		D. pneumoniae, I, II, III, V, VII, VIII, XIV.	(1914)	1. Pneumococcus.
		Streptococci, hemolytic and nonhemolytic.	(1918)	2. Streptococcus.
		Staph. albus and *aureus*	(1914)	3. *Staphylococcus albus.* 4. *Staphylococcus aureus.*
		N. catarrhalis	(1914)	5. *Micrococcus catarrhalis.*
		H. influenzae	(1914)	6. Influenza bacillus.
		K. pneumoniae	(1914)	7. Friedlander bacillus.
		C. diphtheroides	(1915)	8. Pseudodiphtheria bacillus.
	Immunovac Respiratory Vaccine (Parenteral).	Killed bacteria:		Bacterial antigen made from:
		D. pneumoniae, I, II, III, V, VII, VIII, IX.	(1926)	1. Pneumococcus.
		Strep., hemolytic and nonhemolytic.	(1926)	2. Streptococcus.
		Staph. albus and *aureus*	(1926)	3. *Staphylococcus albus.* 4. *Staphylococcus aureus.*
		N. catarrhalis	(1939)	5. *Micrococcus catarrhalis.*
		H. influenzae	(1939)	6. Influenza bacillus.
		K. pneumoniae		7. Friedlander bacillus.
		C. diphtheroides		8. Pseudodiphtheria bacillus.
	Mixed Infection Phylacogen.	Extract solution of:		Modified bacterial antigens:
		E. coli	(1928)	1. *Colon bacillus.*
		D. pneumoniae, I, II, III, V, VII, VIII, and XIV.	(1926)	2. Pneumococcus.
		Staph. albus and *aureus*	(1926)	3. *Staphylococcus albus.*
		Streptococci, hemolytic and nonhemolytic.	)1926)	4. *Staphylococcus aureus* 5. Streptococcus.
	N. catarrhalis Immunogen (combined).	Ectoantigens from:		Bacterial antigens made from:
		N. catarrhalis	(1926)	1. *Micrococcus catarrhalis.*
		D. pneumoniae, I, II and III.	(1926)	2. Pneumococcus.
		H. influenzae	(1939)	3. Influenza bacillus.
		Streptococci, hemolytic and nonhemolytic.	(1926)	4. Streptococcus.
		Staph. albus and *aureus*	(1926)	5. *Staphylococcus albus.* 6. *Staphylococcus aureus.*
	N. catarrhalis Vaccine (Combined).	Killed:		Bacterial vaccines made from:
		N. catarrhalis	(1914)	1. *Micrococcus catarrhalis.*
		K. pneumoniae	(1914)	2. *Friedlander bacillus.*
		D. pneumoniae, I, II, III, V, VII, VIII, XIV.	(1914)	3. *Pneumococcus.*
		Streptococcus hemolytic and nonhemolytic.	(1918)	4. Streptococcus.
		Staph. albus and *aureus*	(1914)	5. *Staphylococcus albus.* 6. *Staphylococcus aureus.*
		C. diphtheroides	(1915)	7. *Pseudodiphtheria* bacillus.
		H. influenzae	(1914)	8. Influenza bacillus.
	Streptococcus Immunogen, Arthritis (Bio. 327).	Ectoantigens from: Six nonhemolytic and three beta hemolytic streptococcal strains.	1918	Bacterial antigen made from streptococcus.
Travenol Laboratories, Inc.	Piromen (Pseudomonas polysaccharide).	Mixture of polysaccharide and nucleic acids derived from pseudomonas.	1952	Pseudomonas polysaccharide.

[1] SPL said to contain live polyvalent staphylococcal bacteriophage and products of bacteriological media.
[2] Year component licensed indicated in parentheses.
[3] BAC=Bacterial Antigen Complex.
*(1955=fecalis; 1928 for remainder.)

The Advisory Panel appointed to review data and information concerning safety, effectiveness, and labeling of Bacterial Vaccines and Bacterial Antigens with "No U.S. Standard of Potency," has completed the review and submitted the following report:

Basis of Evaluation

About a century ago it was established that some diseases were caused by microbes; somewhat later, it was shown that certain infections could be prevented by properly prepared and utilized vaccines. Once these observations were accepted, the pendulum swung from an attitude of skepticism to a belief that it was only necessary to identify the offending microbe, prepare and inject an appropriate vaccine, and a wide variety of diseases could be prevented, ameliorated, or cured. Were this simplistic version of the host-parasite relationship invariably true, "colds," rhinitis, sinusitis, sore throats, pustular acne, bronchitis, recurrent boils, and "intrinsic or infective" asthma would not remain as man's common afflictions.

The bacterial vaccines and antigens reviewed by the Panel are most commonly prescribed for the treatment or prevention of persistent (or recurrent) respiratory, arthritic and skin ailments. They consist of whole bacterial cells or extracts, modified bacterial antigens, altered bacterial toxins, and other material derived from bacteria, which are generally unproven to be related to the symptom-complex in question. It should be emphasized that they were originally developed when acceptable documentation for product safety and effectiveness often consisted of clinical impressions, testimonial evidence, or other anecdotal and equivocal information. Partly because of major scientific and technical advances (e.g., antibiotics,) and partly because standards for well-controlled evaluations are now more stringent than when these products were originally licensed and made available, the Panel was charged to review them for their safety and effectiveness according to current scientific standards.

Since many of the bacterial products and vaccines under assessment are purported to confer immunity and/or ameliorate bacterial allergies, it is appropriate to define the terms "immunity" and "allergy" as viewed by the Panel.

1. "Immunity" may be defined as the ability of the individual to resist or to overcome an infection. This may be innate or acquired. For most infectious diseases, immunity is generally acquired during recovery or induced by the administration of vaccines prepared from inactivated or live microorganisms of modified disease-producing potential or specific antigen(s) derived from them. The purpose of immunization therefore is to provoke a specific immunologic response to a selected microbial agent or its antigen(s) with the expectation that this will result in humoral (protective antibodies in the blood), or secretory, or cell-mediated immunity. While such protection may diminish with time, sufficient residual immunity usually remains so that the individual responds to future exposures to the same stimulus with a rapid return of the immune response because of the heightened reactivity of his antibody forming, phagocytic, and other cells that mediate the immune mechanism.

For those diseases in which the role and manner of immune responses are clearly definable, methods for such prevention have been readily devised. Indeed, safe and effective vaccines with U.S. standard of potency have been produced which, with adequate immunization programs, have been responsible for the marked reduction or elimination of such previously common diseases as smallpox, measles, diphtheria, tetanus, polio, and yellow fever.

Certain infectious diseases present special problems that impede the development of effective vaccines. One such example is infection with salmonella bacteria; the salmonella group of organisms is composed of a multiplicity of antigenic variants or strains numbering in the hundreds. Among the respiratory diseases, the "cold" viruses (rhino-viruses) and pneumococci present a similar problem. Recovery from infection with any one type of organism leaves the person vulnerable to the others.

In addition, antigen-antibody immune mechanisms are not well understood in all diseases caused by microbial agents. Immune responses to some antigens may be absent, meager, or ephemeral. In addition, the pathogeneses of some diseases alleged to be induced by bacteria, e.g., asthma, are poorly understood and in-

fection may play only an insignificant role in their etiology or course. The presence of the organism, or its antigens, may sometimes be adventitious or part of a complex cycle in the evolution of the disease syndrome in question. In certain situations, unfortunately too often in recurrent and chronic infections of the respiratory tract and occasionally of the skin, the exact host-parasite relationships of the presumed offending organisms are so obscure that the factors that determine infection and resistance remain undefined.

Thus, many diseases such as "colds," rhinitis, infectious asthma, uveitis, and rheumatoid arthritis for which treatment with "bacterial vaccines and antigens" is recommended are of unknown etiology or, at best, of obscure pathogenesis. Moreover, diagnoses of these diseases frequently are unsupportable with objective data. Since it has been demonstrated that certain types of treatment are useful in some diseases of unknown cause, it is questionable whether it is always necessary to know the specific etiology of a disease to determine an effective treatment. The need to know the etiology may not apply to the products under review because of the complex natures of their target diseases, often chronic ailments with frequent spontaneous remissions and relapses. Their symptoms are ill-defined and often equally characteristic of many other diseases. Furthermore, as with other illnesses, psychological factors in many maladies for which these products are recommended may be associated with a placebo effect following any therapeutic measure. It also is probable that the populations with these disabilities are heterogeneous because their responses to a given treatment often are unpredictable.

2. "Allergy" is currently defined as a broad spectrum of untoward physiologic events mediated by one or more immunologic mechanisms. Poison ivy and poison oak reactions, serum sickness induced by penicillin or horse serum injections, and asthma induced by exposure to ragweed pollen or dog dander are all considered to be "allergic conditions."

This definition may seem too permissive; but in fact it is very stringent because it requires than an immune mechanism be involved in the immunopathology of the disease. Indeed, its acceptance implies three criteria for establishing the definitive diagnosis of a symptomatic allergic state: (1) Identification of the suspected antigen, (2) proof of a causal relationship between this antigen and the sign or symptom under consideration, and (3) identification of the immunological mechanism involved and its causal relationship to the signs or symptoms. A strict adherence to these criteria would be of great assistance to the evaluations of the pathogeneses of the disease states for which treatment with the products reviewed by this Panel is recommended.

Experts disagree about the relative roles of allergy, infection and immunity as defined by the Panel in such varied diseases as recurrent or chronic rhinitis, uveitis, glomerulonephritis and angioedema.

Areas of Panel Concern

A major problem for the Panel was that the information available often was inadequate to characterize the effects of these products in man. If a product were potent as an antigen it could: (1) Induce immunity, (2) diminish allergy as defined by the Panel, or (3) produce or enhance allergy. Hardly any information could be identified on the use of these products that would permit the establishment of the conditions that favor the first two possible effects over the third.

To complicate the situation further, different microbes vary in their disease-producing capacities. Some accomplish this by an antiphagocytic effect of their polysaccharide capsular material, others by secreting exotoxins (often with the aid of their own parasites) or by releasing endotoxin. Most microbe disease-producing capacities are caused by unknown mechansims. Since numerous microbial agents normally inhabit the respiratory tract, the task of determining whether a particular agent is pathogenic and if so, how often, can be formidable.

In addition, there is reason to believe than once an infectious disease is initiated, vaccine can be no longer effective because it has been proven to be at best a preventive rather than a therapeutic or ameliorative measure. Nevertheless, the Panel discussed the possibility that some infections, such as chronic sinusitis, may represent the combination of an infective as well as an allergic manifestation. Thus repeated injections of a vaccine containing the offending antigen may result in an altered immunologic state and reduction of allergic symptoms. However, this premise remains to be demonstrated.

The Panel concluded that the effectiveness and safety of treatment with a product for a given disease can be judged properly by adequate and well-controlled studies on populations of patients having the most well-defined disease states and carefully selected to be as homogenous as possible. Such studies would demonstrate effectiveness whether the mechanisms of action were by either immunization or desensitization.

Specific Product Characteristics

While all licensed biologics are undergoing reviews for safety, effectiveness, and appropriateness of labeling at this time, the products assigned to this Panel have several characteristics that distinguish them from other categories of vaccines and antigens. Some of these characteristics are:

1. No additional standards or standard measures of potency now exist for any of them. For practical purposes, it could be argued that demonstrated effectiveness of the material in the treatment or prophylaxis of a given disease state a priori is a measure of potency. Nonetheless, the Panel believes that defined standards of potency for these products are necessary to establish that the microbial factors claimed to be present are indeed there and in what concentration. Standards of potency also are required for laboratory tests to evaluate the relative quality of different product lots and to correlate component presence with clinical effectiveness data.

2. A second characteristic of the products reviewed by this Panel is that most were licensed many years before the bacterial vaccines for which there are standards of potency. This is of significance for several reasons:

(a) Vaccines of recent origin were developed for diseases whose specific etiologic agents had been identified and whose pathogeneses had been elaborated. With rare exceptions, this cannot be said for the biologics without standards of potency. When many of the products reviewed within this report were first developed, many of the diseases for which they were recommended were (and some remain) of obscure etiology.

(b) It is apparent that the studies of the newer products were relatively well conducted in terms of scientific methodology, and good information was produced which permits their usefulness or harmful effects to be adequately assessed.

(c) The specific information available for these biologics is inadequate. This includes frequently unstated rationales for (1) Selecting component bacterial strains and their etiologic relationships, (2) justifying the use of multiple bacterial species derived from normal respiratory flora, (3) selecting a particular method for product preparation that influences its ultimate quantitative and qualitative antigenic contents, and (4) recommending dosage and treatment schedules.

3. The third characteristic is a lengthy history of use. The Panel attempted to identify information that would corroborate the testimonial evidence and unconfirmed and uncontrolled clinical impressions that it received from both producers and individuals. Alternative methods for adequate and well-controlled studies were considered and have been described (21 CFR 314.111(a)(5)(ii)). Among these were animal studies, laboratory assay methods, serological responses, and historical controls. None of these alternatives was considered to be sufficient to establish definitive effectiveness, for reasons that will be discussed later.

Safety

A recurring question about safety comes from the recommendation that the "bacterial vaccines and antigens" under review be administered (usually parenterally) repetitively over extended periods of time. Claims for safety were based primarily upon the manufacturers' reliance on long marketing experience and infrequent physicians' reports of adverse reactions. This might have been satisfactory had there been some evidence of systematic followup by physicians for the late, and perhaps subtle, adverse effects that might be associated with repeated inoculations.

In view of what is known from laboratory studies about the potential risks associated with repeated inoculations of foreign substances, the Panel was left with reservations about the long-term safety of the subject products.

Another question of safety that surfaced repeatedly, as individual items were reviewed, was their use in pediatric populations. Specifically, only the most limited information was available to provide the basis for dosages, routes, and recommended repetitive usage in children.

Panel Specific Product Reports and Reviews

More detailed analyses will be found in the Panel's general position statements and specific product reports. The problems may be summarized as follows:

1. The etiologies and pathogeneses of many conditions treated with "bacterial vaccines and antigens" and the way in which they might prevent or alleviate the pathologic state are not well understood.

2. The causal relationships of the species or strains of vaccine organisms (or derivatives) to the diseases for which they are prescribed are generally unclear.

3. Standards of potency are needed, including precise identification of the contents of the finished products.

4. Patients treated for many of the recommended conditions represent highly heterogeneous subgroups whose conditions and symptoms are noticeably labile and difficult to characterize objectively. These subpopulations should be defined and identified.

5. Data on the rate and significance of spontaneous remissions in the chronic disorders for which these products are used are not available.

6. The rationale by which the selection of bacterial strains for incorporation into a given product often was either not clear or not stated.

7. The need to include different bacterial strains (and species) into one vehicle was not documented.

In reviewing the submitted data and preparing its report, the Panel applied the definitions of standards for safety, effectiveness, and labeling that are specified in the regulations governing the review procedures under which its report was prepared (21 CFR 601.25(d) (1) through (5)).

The Panel cannot recommend waiver of these requirements on the basis of claims that a controlled clinical trial is not feasible because of lack of funding, lack of interest, or difficulty in obtaining a sufficient number of patients.

In essence, three basic questions were asked by this Panel for each product reviewed:

(1) Does the final product, as administered to the patient, contain the active ingredients that are said to be present?

(2) Has the active substance been clearly shown to be safe in a defined population?

(3) Has it been clearly demonstrated that the active agent is effective for specified indications under defined conditions?

Theoretically, it may not appear difficult to outline a set of scientifically sound criteria with which to determine the safety and effectiveness of a preventive or therapeutic agent. Practically, this has been relatively easy for some products, for example, poliovirus vaccine. This has not been done for most of the products under consideration in this review; the development of such criteria constitutes a formidable but mandatory task.

Panel Recommendations and Conclusions

Because evaluation of the questions cited above may be beyond the capability of some of the manufacturers involved, the Panel recommends to the Commissioner of Food and Drugs that the Federal Government undertake or sponsor some of the required studies. This recommendation would be consistent with the review procedures as described in the Code of Federal Regulations (21 CFR 601.25(h)(1)), which state that "the Federal Government may undertake the studies." This recommendation is made because of concern that there may exist a subpopulation of patients that might conceivably benefit from these products. Another reason for Federal support for research in this area is that data resulting from some of the more recent studies conducted with a few of these products may be interpreted to indicate that cell-mediated immunity may be altered by the use of bacterial vaccines. Such information, if verified, could have some theoretical implications for the future use of some of the products under review.

The Panel realizes that research in this area would compete for Federal sponsorship with many high-priority research areas, but if a large number of illnesses are indeed allergic states caused by bacterial antigens, then this too is a high-priority area. It is estimated that 15 percent, or more than 30 million Americans, experience significant allergic illnesses and that at least 4,000 deaths a year may be attributed to asthma. Hospitalization costs for 1972 were more than $60 million for allergy-related sicknesses and close to $150 million are spent for prescription drugs to treat allergic diseases annually. Thus the illnesses for which the products under review are used are not insignificant in terms of morbidity, disability, mortality, and cost.

The Panel on Review of Bacterial Vaccines and Bacterial Antigens with "No U.S. Standard of Potency" evaluated the data submitted in support of the licensure of each of the products listed in Table 1 in this preamble.

After completing a product-by-product review, the Panel assigned each product to one of the following three categories required by existing regulations (21 CFR 601.25(e) (1) through (3)):

Category I. Biological products determined to be safe and effective and not misbranded.

Category II. Biological products determined to be unsafe, ineffective, or misbranded.

Category III. Biological products determined not to fall within either Category I or II on the basis of the Panel's conclusion that the available data are insufficient for their classification and for which further testing is therefore required. For those products judged to be in Category III, the Panel was asked to recommend whether their licenses should be retained (Category IIIA) or revoked (Category IIIB) while adequate data concerning safety and effectiveness are generated under controlled conditions. The product license will not be revoked "where the Commissioner determines that the potential benefits outweigh the potential risks" under § 601.25(f)(3) of the regulations (21 CFR 601.25(f)(3)).

The discussions that follow include a series of position statements that form the basis for the Panel's recommendations and the detailed individual reviews of each product. Generic-type assessments were attempted, but the Panel concluded that most of these products were essentially single-class items and did not readily lend themselves to such groupings. The Panel concluded that for specific products for which there are little or no data, it would be unwarranted to assume a generic similarity to those for which there might be sufficient data to permit their retention pending the completion of further evaluations. The safety and effectiveness of biologic products can be significantly affected by variations in, for example, the bacterial growth media used; the sources of seed cultures and the strains used; the methods of growing, harvesting, and inactivating the organisms used for biological products; and the method of preparing the final product. If data for a specific product are lacking, benefit-risk assessments cannot be made objectively, leaving the Panel with no alternative but to recommend its removal pursuant to § 601.25(e)(3) of the regulations.

Therefore, the Panel recommended that some products be allowed to remain on the market pending completion of additional tests and that others, which may superficially appear similar, have their licenses suspended pending the completion of further studies. In any case, the Panel is unalterably opposed to the future use of any product of imprecise nature and strongly recommends that action be taken to assure that standards of potency will be developed within a reasonable period for those items whose continued availability is permitted.

The Panel has arrived at these decisions after much discussion and thought. In categorizing products, it risks leaving the impression that it is unaware of current research in the development of new vaccines for some organisms which are included in these products, such as *H.*

influenzae, type b, pneumococci, the M-proteins of Group A beta hemolytic streptococci and others.

The cross antigenicity between organisms and shared antigens has been shown to have a potential for benefit as well as for adverse effects. An example of potential benefit could be the shared antigenicity between certain strains of *E. coli* and *H. influenzae*, type b. There is currently research interest in using this cross antigenicity as the basis for producing better immune responses to *H. influenzae* vaccines. This then, could provide a rationale for testing the effectiveness of *E. coli* in certain preparations where its presence at first might seem illogical. This same relationship may be expanded to include many other shared antigens.

The Panel also is cognizant of the wide spectrum of immunological capabilities and sensitivities that all persons possess. Current research suggests these may have a genetic basis, which could explain the variation in therapeutic responses suggested by some of the clinical impressions of the effects of the vaccines.

The intense activity that currently characterizes the fields of immunology, microbiology, and genetics may lead to clarification of the contradictions and obscurities in the usage of bacterial vaccines for the disorders for which they were devised and recommended in the past.

EXTENT TO WHICH PRIOR USE OF THESE PRODUCTS CAN BE USED TO SATISFY PRESENT STANDARDS OF SAFETY AND EFFECTIVENESS

Justification for placing products in Category IIIA is presumptive evidence of effectiveness and safety. Although not clearly stated, the implication is that such suggestive evidence can be largely derived from the fact that many of the products have been widely used for many years and that although systematic rigorous trials may not have been done, the lack of reported dangerous side effects over a period of many years indicates in itself at least a certain degree of safety. Effectiveness can be looked at in the same way, in that continued use over many years by licensed physicians would presume some degree of effectiveness.

These contentions are quite reasonable, provided there is some evidence to show that the product, in fact, has been widely used, that careful clinical judgment was exercised, and that adverse effects, if present, would have been reported. The crucial task presented to the Panel then became an evaluation of the strength of the data that have accumulated as a result of the widespread human use in the years between initial licensure and recent revision of standards. The purpose of this position statement is to describe the considerations used by the Panel in evaluating the validity of past use as a measure of safety and effectiveness. It has been prompted in large part by the expressed fears of many practicing physicians that Panel members will make arbitrary decisions and that the findings of doctors who have used these biologicals for many years will be discounted without careful consideration. This is not the intent of the Panel, and one purpose of this statement is to allay any such fears.

DETERMINATION OF USE

Compilations of testimonials from practicing physicians do indicate some degree of acceptance and are of value to the Panel, but their significance is limited. Other measures, also of limited significance, which have been considered by the Panel, are sales volume, recommendation both in standard medical texts and by study groups of specialty societies, and use in teaching hospitals. This information, with the exception of sales volume data, is available from the files of this Panel and can be viewed on request at the office of the Hearing Clerk, Food and Drug Administration.

EFFECTIVENESS

For the biologicals which this Panel reviewed, the bulk of the effectiveness data consists of either statements by individual physicians, collections of case reports, or uncontrolled clinical trials.

In evaluating these biologicals, it is essential to keep in mind that there are two basic questions involved in determining their effectiveness. These are clinical judgment and causal relationship:

1. *Clinical judgment.* Is the evidence that an effect occurred following administration of a biological based on sound clinical judgment?

(a) Is the determination of response based on objective data? Impressions gained solely from subjective patient responses may be valuable in certain circumstances, but are less useful to the Panel than objective criteria.

(b) Have the clinical findings been systematically recorded? General unsupported statements stating only that "good clinical responses were obtained" were reviewed by the Panel as additional evidence, but could not be used to support effectiveness (see 21 CFR 601.25(d)(2)).

2. *Causal relationship.* Is the clinical effect causally related to the action of the product? In the absence of double-blind and placebo-controlled trials, other factors can be used to make judgments on causal relationships. Specific questions the Panel considered were:

(a) What is the natural history of the disease to be treated? This critical question to a large extent determines the need for controlled studies. Certainly, when a disease has a uniformly poor prognosis and administration of a biological improves the clinical state, a causal relationship can be inferred on the basis of clinical data alone. On the other hand, some diseases are subject to frequent spontaneous cure or remission and others are known to be strongly influenced by psychologic factors. It is for these that controlled studies are necessary since clinical judgment alone cannot determine causal relationships.

(b) Are the results reproducible? Data obtained by a single study or investigator, regardless of competence, can only be considered suggestive.

(c) How strong is the association? A marked and uniform association of clinical response with administration of a biological gives greater confidence in inferring a causal relationship.

(d) How specific is the association? Biologicals may have diverse effects, but one that appears to do all things for all people must be regarded with some suspicion.

(e) Are the beneficial effects observed derived from other therapeutic measures being carried out simultaneously with administration of the biologic products?

(f) Is the explanation for its effect plausible? A clear scientific basis, although not essential, gives strength to the assumption of effectiveness of any biological.

SAFETY

It could be logically presumed that physicians would not continue to use any biological that has an obviously unfavorable risk/benefit ratio. The problem faced by the Panel, however, is that safety or danger can be viewed as a matter of degree, and that lesser degrees of danger may not become obvious under normal conditions of use. There are several possible reasons for this inability to recognize dangerous effects, all of which must be considered by the Panel and weighed for each biological under review. These are:

1. There is no effective mandatory system for the reporting of adverse reactions. Under-reporting has been documented for a wide variety of products, and its existence must be assumed.

2. The practicing physician sees only a limited number of patients and will identify only adverse reactions that occur at a high rate, even if he can retrieve information from all patients. The accumulation of reports from a single practice might not uncover reaction rates as high as 1:1,000.

3. Patients with severe reactions may not return to the same treatment situation, further diminishing the likelihood of discovery and reporting. While well-designed clinical trials make provision for followup of dropouts, this situation is generally not feasible in any individual private practice.

4. If adverse reactions show varied clinical manifestations, as may be seen in immunopathologic conditions, it is more difficult to recognize their relationship to the administered biological.

5. The likelihood of noticing a causal relationship is inversely related to the elapsed time between the administration of a biological and the onset of adverse effects. This point becomes of particular importance in judging possible long-term consequences.

6. Adverse reactions that are exaggerations of already present symptoms of the clinical state being treated, or which mimic them, are less apt to be noted and reported as adverse reactions. Instead,

they may be regarded as natural consequences of the disease being treated.

All of the above features have been considered by the Panel, since all tend to reduce the likelihood of becoming aware of possible adverse or dangerous effects. It also should be noted that the reverse situation, i.e., reported associations of adverse effects with biologicals, must be subjected to the same type of scrutiny. The appearances of untoward symptoms at or near the time a biological product is administered does not in itself establish a causal relationship. The same causal factors must be considered as were addressed above concerning effectiveness.

SUMMARY

Many factors are used to evaluate safety and effectiveness, only one of which is many years of prior use without recorded ill effects.

1. The fact that a biological has been used for many years does not of itself provide the basis for continuation of usage under new standards. Rather, the circumstances of its use must be examined. For illustration, two extremes can be considered:

(a) A biological may have demonstrable widespread acceptance and use; the natural history of the disease for which it is employed is predictable and relatively uniform; the clinical picture is well documented by modern clinical standards; and systematic observations of possible side effects have been made. Under such circumstances, the Panel could regard the intervening years of use as providing an acceptable indication of safety and effectiveness, despite lack of extensive double-blind controlled trials.

(b) A biological has been used at a low frequency rate in conditions that have high rates of spontaneous variation in which clinical effects cannot be objectively determined; the period of usage would have little influence on present safety and effectiveness considerations.

2. There is no simple answer to the question as to how much the Panel should ascribe to the prior experiences of practicing physicians. Such extensive physician experience is of considerable importance and has been carefully considered. Any just and fair recommendations must be based on skills from a variety of disciplines and should reflect no single outlook or attitude. The Panel considered the data available from all sources, carefully weighing and balancing the various points of view in an effort to arrive at just and fair recommendations.

DIFFERENTIATION BETWEEN PRODUCT STANDARDS AND POTENCY

Most of the bacterial vaccines and antigens with "No U.S. Standard of Potency" originated when taxonomic classifications based upon morphology, motility, colony characteristics, growth requirements, metabolic patterns, and staining properties were the principal means available for the identification of microorganisms. Virulence in humans and/or animals sometimes provided an additional parameter for identification. Standardization of contents usually was based upon the initial number of organisms per milliliter that went into the production of the product.

The conditions under which the strains of bacteria were maintained in the producing laboratories have not always been such as to ensure stability of their biological characteristics. Multiple transfers on artificial media provide opportunities for changes among the bacteria thus propagated. It has become apparent with the accumulation of knowledge of the capabilities of microorganisms to mutate, to transfer genetic material sexually and to form protoplasts, and as unique products such as specific carbohydrates, proteins, lipids, toxins and endotoxins have been more precisely defined, that there must be concern with far more than the number of dead cells (or products thereof) that are in a given volume of a vaccine or antigen.

Effective standardization of content does not necessarily guarantee "potency." Potency is legally defined in 21 CFR 600.3(s) as follows:

> The word "potency" is interpreted to mean the specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect a given result.

Thus potency may be distinct from ability to prevent, ameliorate, or modify in a beneficial way a disease state (effectiveness). For example, a given antigen may induce specific antibodies after a specified interval of time when administered in a specified fashion. Whether such antibodies prevent or alter the course of disease is a separate problem. To illustrate, agglutinating antibodies induced by the antigen may be found not to correlate with the prevention or modification of a given disease state. On the other hand, serum neutralizing antibodies might follow the natural disease, but not administration of the antigen, and correlate strongly with the ability of the host to recover from or not to acquire a particular disease. Thus evidence that a substance is potent as an immunogen would be insufficient to support effectiveness, unless a previously established correlation existed.

Potency is an extremely important aspect of the consideration of bacterial vaccines and antigens for which there are no U.S. standards. The primary attribute, of necessity, is that these substances be so safe as not to cause more harm than benefit. The third desired characteristic is effectiveness, but usually all three aspects are interrelated. Thus it would be unreasonable to assume that a vaccine or antigen of inadequate potency would be effective, except perhaps for a placebo effect. Consequently, the establishment of potency is second only to safety among the requisite attributes of vaccines and antigens and when possible should precede attempts to determine effectiveness. Exceptions, if any, can be dealt with on an ad hoc basis.

How should potency be assessed? First, it would seem reasonable to expect and to require that whatever biologically active ingredients are stated to be in a biological product are indeed present. In addition to this qualitative determination, it is also necessary to know the concentration of active ingredient(s) present. As a consequence, general statements by themselves that a vaccine or antigen contains "those products which result from the dissolution of bacterial cells" are unacceptable. The substances considered to be germane to the proposed function of the product should be identified as precisely as is consistent with current knowledge. The statement concerning their identification should be accompanied by some quantitative estimate of their presence in the vaccine, however that estimate is determined. Whenever possible, this should be on an absolute weight basis; otherwise, it may be in terms relative to some reference substance (activity) or even in concentrations determined with a reproducible dilution system. Since the belief that these products are biologically active is implicit in the fact that they are marketed and used, some indications of the effects of the material in animals or man are required. Determinations of effectiveness ultimately must be performed in humans who are at risk of acquiring the defined disease state for which the product was devised if it was meant to be preventive, or who have the disease if the product was meant to be ameliorative or curative.

For some of the products for which there are no U.S. standards, the matter of potency is doubly complicated by their recommended usage as both immunizing and desensitizing agents. These apparently quite different functions demand quite different approaches and tests for potency evaluation, although that of immunization or protection is not as complicated as is that for desensitization. For the latter, presumably one is dealing with diseases in which an allergic reaction to an antigen is the keystone of pathogenesis. The function of the desensitizing substance presumably is to diminish the amount of antibody or other receptors either attached to or contained within sensitized cells. For safety, the antigen dose which can be administered to the host without ill effects, per se, or aggravating the disease, must be determined by trial and error during the desensitization process. The same conditions pertain for the determination of the therapeutic dose.

There is no suitable animal model for most of these human diseases, and in vitro testing has not produced acceptable standards of potency for clinical use of any product. Until such standards are developed, proof of clinical effectiveness may be the only reliable evidence for potency.

From the foregoing, it is evident that single component or single purpose products are more readily evaluated as to

their potency than complex, multipurpose, multicomponent vaccines. It can be anticipated that there will be a direct relationship between the number of components said to be present in a particular biological product and the difficulty in establishing the "potencies" of these components, individually and in combination. Moreover, without such determinations it is difficult, if not impossible, to determine shelf life. While it might not always be possible at any given stage of development to establish the potency of each assumed component of a vaccine, some must be measurable and standards for them should be set. Ultimately, this will not only have to be done product-by-product, but component-by-component as well. Otherwise, the products remain in continued use without reason or substance, raising false expectations on the part of both physician and patient for prevention, amelioration, or cure. Until products of reproducible composition are available, it would seem impractical to consider mounting human trials of effectiveness.

Standardization of Vaccine or Bacterial Product Content

To standardize the contents of these biological products, the following shall be required:

1. All bacteria (or the products thereof) that are incorporated into "bacterial vaccines and antigens which have no U.S. standard of potency" shall be identified in accordance with the nomenclature employed in the current edition of "Bergey's Manual of Determinative Bacteriology", Williams and Wilkins, Waverly Press, Mt. Royal and Guilford Avenues, Baltimore, Md. For the present, the designations of specific strains hitherto in use should parenthetically follow the definitive species name. Because of the constraints of printing space, these parenthetical designations would not be required on the label, but would appear in the package insert and in descriptive records supplied to the Bureau of Biologics, Food and Drug Administration. It would be expected that justification for the use of specific strains would be available on request; that is, evidence that a particular strain yields a product(s) that is (are) more useful in a given circumstance than other members of the same species.

The use of standardized nomenclature should make the product's contents more readily discernible to the physician who prescribes it, in articles in the scientific literature, and for those persons charged with maintaining surveillance of the product's safety and effectiveness.

2. Seed and reference cultures shall be maintained under conditions that favor stability of their biologic characteristics using such methods as lyophilization or storage in liquid nitrogen.

3. The bacterial strain used shall originate from a well-defined source, e.g., the American Type Culture Collection, and be maintained within a circumscribed number of passages and in such a way that periodic comparisons with the original source can be made to determine variations. If changes are recognized, manufacturing seed lots will be replaced from the original seed.

4. Contents will be defined in quantitative, physical, and chemical terms; biologic activity shall be estimated by suitable in vitro or in vivo systems to ensure that conditions of growth or processing have not resulted in undesired alterations in the final product.

5. The possible interactions of active components in a mixed vaccine shall be evaluated to determine whether they potentiate or vitiate each other's properties.

6. Preparations that do not contain whole bacteria, but rather one or more products or antigenic components of the bacteria from which they are derived, shall have similar standards applied as for whole bacterial vaccines. Their sources shall be clearly designated, their characteristics fully described and recorded, and their biologically active principles defined in either or both chemical and biological terms according to generally recognized standards.

Potency

The following shall be required for the establishment of potency:

1. The biologically active ingredients said to be present in a vaccine or antigen shall be enumerated. This includes substances that are assumed to be present but for which proof of identity is either lacking or not possible.

2. Methods for detecting and measuring each identifiable ingredient said to be present in the vaccine or bacterial product shall be provided. If this is not possible, a reasonable explanation shall be offered.

3. Methods for estimating the biological activity of each measurable ingredient, both individually and in combination, under suitably controlled conditions shall be provided.

4. The methods mentioned above shall be applicable to determinations of the durations of biological activities under various conditions of storage such as temperature, light, suspending vehicle, container characteristics, air, etc. The effects of the incorporated preservatives on the activities of the components of the vaccine shall be estimated similarly. This implies validation of the expiration date on the label, which indicates that the vaccine was "active" to that time.

Safety of Bacterial Vaccines and Products

The "Virus and Serum Toxin Act" of 1902, the first of the laws regulating biological products, was passed as a result of deaths following the use of contaminated diphtheria antitoxin. The first laws regulating food, drugs, and cosmetics followed in 1906 to stem adulteration and misbranding of food and drugs by producers. Modifications of the original acts have since occurred as the direct result of tragedies following inadequate testing of drugs and/or drug vehicles.

Safety, as it relates to bacterial vaccines and bacterial products, indicates absence from harmful effects on persons, directly or indirectly. Biological products, by their nature, must be considered to have a potential for danger. For example, no information was provided on the presence or absence of bacteriophage or its residual antigen(s) at any stage in the manufacturing process, except for one product.

In late 1972, Merril and associates first isolated bacteriophage (*E. coli*) from commercial lots of bovine serum used to support tissue culture growth of attenuated live virus vaccines (Ref. 2). This information increased the general concern about the purity and safety of viral vaccines, actually or potentially contaminated by viruses such as SV40 (endogenous), bovine herpes virus (exogenous), and coliphage, the latter from a slaughterhouse contaminant, *E. coli*. These problems were summarized recently by Hopps (Ref. 3). She discussed the malignancy risks of certain endogenous viruses and bovine herpes virus, the latter being a malignant transforming effect on hamster embryo cells similar to that of the human herpes virus (Ref. 4). By contrast, no one has demonstrated any such effects from any bacteriophage, although Merril (Ref. 5) used the results of two preliminary studies to support his concern about the interaction between bacteriophage and mammalian cells. In one, published over 10 years ago, Mankiewicz reported that myco-corynebacteriophages isolated from patients with lung cancer were cytopathogenic for HeLa and African green monkey renal cells in tissue cultures (Ref. 6). In the second report, a brief abstract, Schechtman et al. found that T7 bacteriophage and phage DNA were taken up by the nuclei of hamster cells in culture (Ref. 7). No evidence of malignant transformation has emerged.

Another of Merril's concerns was the possible conversion of bacteria into pathogenic forms by phage. Perhaps the best example is the conversion of *C. diphtheriae* into a toxin-producing form after infection with its βphage (Ref. 6). Whether any of the products under review might contain such a class of phages is doubtful but not completely ruled out.

The Panel recognizes that, except for the limited examples of bacterial transduction, no harmful effects of bacteriophages in man have yet been recognized, despite the extensive use of bacteriophages in therapy before the antibiotic era (Ref. 8). Furthermore, there is constant contact with phages throughout the life of man (but not by parenteral administration). Finally, immunological studies in infants and immunodeficient subjects given coliphage X174 have revealed no adverse effects (Refs. 9 and 10). Yet the Panel shares the concern expressed by Hopps who, after acknowl-

edging the lack of adverse information for man (Ref. 3), stated:

> Nevertheless, whether on account of theoretical risks for man, from the public health point of view, or because of the possible interaction of phages with cell cultures used in research, the exclusion of these agents seems desirable.

Exclusion may not, in fact, be attainable, particularly in the case of staphylococci. Perhaps all strains of pyogenic staphylococci are lysogenic and thus carry phage (Ref. 11); phage cannot be eradicated from a true lysogenic strain (Ref. 12). Thus it must be assumed that phage or phage precursors are present in the starting materials for several products; consequently, the Panel shares the admittedly theoretical concern about the possible adverse effects of long-term parenterally administered live bacteriophages.

The Panel notes cross-reacting antigens have been described among a variety of widely separated phylogenetic groups. This phenemonon was first reported at the turn of the century with the demonstration of antisheep and antigoat hemolysins in rabbits immunized with ox erythrocytes (Ref. 13). Such observations were extended to include the cross-reaction of red yeast with gram-negative organisms (Ref. 14) and the demonstration of sheep hemolysins in rabbits immunized with guinea pig tissues by Forssman (Ref. 15).

Since that time, cross-reacting antigens have been described between bacteria and mammals, including antigens shared by human Group A red blood cells, the Shiga and paratyphoid bacilli, the pneumococcus, and human Group O erythrocytes (Refs. 16 and 17). The demonstration of cross-reactions between Group A streptococcal antigens and human heart muscle (Refs. 18 and 20) stimulated conjecture about the part played by such cross-reactions in autoimmune diseases. The discovery of the transplantation and antigen-like properties of Group A streptococcal cells extended the concept of cross-reacting factors from humoral to delayed hypersensitivity systems (Refs. 21 through 23).

Rowley and Jenkin (Ref. 24) described the antigenic similarity between *Salmonella typhimurium* and mouse tissues resulting in the extreme susceptibility of mice to infection with *S. typhimurium*. Rats, on the other hand, were found to be resistant to such infections. Utilizing mouse and rat peritoneal macrophages, these authors demonstrated that phagocytosis and killing of *S. typhimurium* by mouse macrophages was minimal after treatment of the bacteria with normal mouse sera, whereas treatment with rat sera resulted in appreciable phagocytosis and markedly reduced bacteria survival.

These observations were extended further in an experiment demonstrating Salmonella clearance by the reticuloendothelial system of normal mice before and after opsonization of the bacterial cells with rabbit antiserum to mouse tissue. This data suggested that antigens shared by mice and *S. typhimurium* make mice susceptible to infections whereas opsonization of *S. typhimurium* by antimouse tissue antibodies ablated the effect of tolerance. Other evidence to support this hypothesis was reported by Simonsen and Harris (Ref. 25), who found that turkeys (normally resistant to Rous tumor virus) immunized with chicken (the natural host of Rous virus) red blood cells during embryonic life, became susceptible to the Rous tumor virus.

The demonstration of blood Group A activity in variola (smallpox) virus and blood Group O activity in *Yersinia pestis* (Pasturella) prompted attempts at correlating the presence of blood group distributions in certain geographic areas with epidemics caused by these agents. This hypothesis by Pettenkofer (Ref. 26) that persons with blood Group A or O are susceptible to infections by these pathogens on the basis of being unable to respond because of tolerance, has been vigorously disputed (Ref. 27). Nonetheless, a case has been made for cross-reactive antigens playing a part in host-parasite relationships and in phylogeny.

The repetitive administration of bacterial antigens to patients raises questions of safety that are both real and demonstrated as well as hypothetical. The presence of ABO blood group cross-reacting antigens in bacteria is of clear-cut danger in the induction of isoantibodies capable of producing hemolytic ABO reactions in newborns (Ref. 28).

Theoretical considerations for which there is supporting evidence leading to some concern may be seen in instances of cross-reactions between Group A streptococcal cytoplasmic and human glomerular membranes (Ref. 20) and in reports of white graft reactions by Rose and Rapaport (Ref. 28) in patients with Group A streptococcal and staphylococcal infections who received homografts.

The hypothesis proposed by Mekler (Ref. 29) to explain the clinical manifestations of influenzal infection suggests that the incorporation of host DNA into the process of viral replication results in a viral membrane bearing host antigens. Given this sequence an antibody response potentially could produce a variety of auto-immune complications.

Studies of cross-reacting antigens in auto-immune reactions suggest that new (or previously unrecognized) problems may follow the injection of patients with some bacterial and viral preparations.

Springer (Ref. 30) described the development of immunologic incompatibility between mother and fetus following immunization of a mother with blood Group O substance and with bacterial and viral antigens with A or B blood group activity.

Lyampert (Ref. 31) cites a report in the Russian literature of experimental evidence for fetal damage after the immunization of the mother and fetus with microbial antigens corresponding to organ-specific antigens.

Many of the organisms present in the vaccines and antigens reviewed by this Panel have been demonstrated to contain cross-reacting antigens. Thus the possibility that cross-reacting substances may induce serious auto-immune reactions must be considered in weighing their benefit and risk potentials. The demonstration of white graft reaction after streptococcal and staphylococcal infection (Ref. 28) has been noted and is of interest relative to the potential for cross-reactive immune phenomena. However, the Panel, in considering that a long history of staphylococcal immunization exists without any of the signposts described for the Group A streptococci, chose not to recommend the deletion of all staphylococci from the products under discussion.

It is noted however, that the same concerns expressed relative to repeated injections of foreign material apply to the vaccines and antigens containing staphylococci.

Endotoxin, the toxic principle produced by gram-negative bacteria, is a constituent of the gram-negative cell wall composed of polysaccharide, lipid and protein referred to as the endotoxic complex. This complex is released into the surrounding medium when organisms are lysed or disintegrated. Endotoxins are produced by a variety of the Enterobacteriaceae, both pathogenic and nonpathogenic. The interest in endotoxin dates to the late 19th century and is the direct result of the many biologic activities ascribed to the substance.

In 1893 typhoid endotoxin was described as having high pyrogenic activity (Ref. 1). Following the introduction of malaria infection in the treatment of patients with tertiary lues (CNS) in the early 1900's, endotoxin (killed endotoxin-producing bacteria) was used in the induction of artificial fever in the treatment of lues and in chronic inflammatory processes.

In 1893 Coley described the tumor necrotizing effect of endotoxin (Coley's Toxin). This effect of endotoxin has prompted such tumor therapy in recent years but the uncontrollable side effects have militated against its extensive use in therapy.

Nonetheless, the many biologic effects of endotoxin have been the subject for research and speculation. As described by Ivan Bennett,

> • • • this spectrum of activities makes possible at least one prediction: an investigator in almost any biological field is likely to obtain a "positive" result if he tries endotoxin in the experimental system he is using.

Over the years much has been done chemically in defining the chemical nature of the biologically active fraction (endotoxin) Lipid A, the product of dilute acid treatment of cell-wall glycolipid, which has been shown to have all of the biologic capabilities of endotoxin listed below.

Pyrogenicity
Lethal toxicity
Toxicity increased by adrenalectomy
Toxicity increased by BCG pretreatment
Shwartzman phenomenon
Bone marrow necrosis
Embryonic bone resorption

Leukopenia
Leukocytosis
Depression of blood pressure
Tumor necrotic activity
Enhanced dermal reactivity to epinephrine
Adjuvant activity
Mitogenic lymphocyte stimulation
Induction of IgG synthesis in newborn mice
Macrophage activation
Colony-stimulating factor
Complement activation
Hagemann factor activation
Plasminogen activator
Induction of prostaglandin synthesis
Induction of interferon production
Nonspecific resistance to infection
Early refractory state to endotoxin pyrogenicity
Induction of endotoxin tolerance
Limulus lysate gelation

These many biologic effects coupled with clinical correlates of endotoxin-induced clinical disease raise serious question of the safety of injecting "endotoxin active" material into humans.

The tumor necrotic activity, induction of interferon production, induction of tolerance weighed against the presumptive clinical correlate of the general Shwartzman-acute cortical necrosis renal) and the many other adverse effects of endotoxin make benefit-risk judgments critical in the use of agents containing "endotoxic activity." The place of such agents rests with carefully controlled studies where apparent benefits clearly outweigh monitored risks. The Panel considering these facts has made its judgments of each individual product in which the potential for endotoxic activity exists.

The Panel also notes that the Advisory Panel on Review of Skin Test Antigens has discussed the problem of thimerosal-induced positive skin reactions (summary minutes, June 6–7, 1975, item 6). This Panel concurs, in general, with the concern expressed therein about the use of a preservative in biological products which are used for skin tests and may induce skin reactions of unknown mechanism in some recipients. This Panel also concurs with the recommendation of the Skin Test Antigen Panel that efforts be initiated to use, or develop if necessary, safe and effective preservatives that do not induce such reactions.

The problem of comparing benefit and risk in these agents presents another parameter and an additional problem in assessing safety in that linking benefit-to-risk introduces and ties effectiveness to safety. In reviewing this problem, the Panel has been guided by the consideration that the public interest is not served by allowing the use of products with high danger potential, or by denying it the use of beneficial agents. Meaningful measures of effectiveness and safety, therefore, must be established if one is to equate or relate benefit-to-risk effectively.

General Considerations for Safety Testing

Investigations of safety of a given bacterial vaccine or product are subject to the same principles as are investigations of effectiveness (Ref. 1). Ideally, tests for safety should be specific and relate to human toxicity. In reality, however, animal studies relevant (or possibly relevant) to safety must be considered in preliminary product assessment. Product sterility, reproducibility, purity, uniformity, consistency, and stability among (bacterial) biological agents are as important in assessing safety as in effectiveness.

1. *Sterility.* Sterility of each lot of each vaccine shall be demonstrated as described in § 610.12 (21 CFR 610.12). Provisions are made for:

(a) Anaerobic and aerobic cultures using Fluid Thioglycollate Medium incubated at 30–32°C.

(b) Aerobic cultures using Soybean Casein Digest Medium incubated at 20–25°C.

(c) Culture of products with mercurial preservative in Fluid Thioglycollate Medium (anaerobic and aerobic) incubated at both 30–32°C and 20–25°C.

(d) Membrane filtration for water insoluble products (U.S. Pharmacopeia, 18th Rev., 1970, pages 853–854) with exceptions as prescribed in § 610.12(f) (21 CFR 610.12(f)).

(e) Different sterility tests as individually outlined.

(f) Different tests equal or superior.

2. *Purity.* Purity of product shall conform to criteria set forth in § 610.13 (21 CFR 610.13).

3. *Additives and constituents.* Provision for additives and constituent material are cited in § 610.15 (21 CFR 610.15).

4. *Storage and maintenance.* These criteria are designed to cite storage requisites for the retention of initial characteristics of the organism and ensure freedom from deterioration as described in § 610.18 (21 CFR 610.18).

5. *Animal testing.* The regulations require a general safety test that is designed to demonstrate acute toxic effects of each lot of all products intended for administration to man (21 CFR 610.11).

(a) Recognizing the vagaries of animal testing associated with dose, and the relationship and significance of tests when applied to man, the Panel suggested that a subcommittee of the various panels on biologics consider the common problem of animal testing. This subcommittee met on February 21, 1974, and noted that special problems exist with products that are repetitively or chronically administered. It was recommended that criteria be considered for chronic animal testing of such products. As such, the Panel recommends that a study designed to establish guidelines for chronic toxicity testing in animals be undertaken under the auspices of the Bureau of Biologics.

(b) In addition to tests for general safety, toxoids are subject to tests to ensure detoxification relative to hemolytic, dermonecrotic, and lethal effects (Ref. 32).

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A Specific Evaluation of the Benefit-to-Risk Ratio on the Use of Group A Streptococcal Antigens in Certain Vaccines and Antigens in Humans

The association of the Group A streptococcus with a variety of pyogenic infections and postinfectious conditions is now well accepted. The history of these associations and the characterization of attempts to establish immunity in humans has been carefully chronicled by Gill (Ref. 1 below). However, the problems that confronted early workers who identified an organism that could be causally related to a clinical disease entity continue to plague present day workers in developing effective and safe vaccines. The classic studies by Dick, Schultz and Charlton (Ref. 2), in the pathogenesis of scarlet fever and the definition of the basic mechanism by Zabriskie (Ref. 3) provide some insight into the multifaceted challenge presented by the Group A beta hemolytic streptococcus and its extracellular products in the pathogenesis of disease.

Almost 100 years have elapsed since Pasteur's description of a chain-forming coccus in his discussion in 1879 of puerperal sepsis (Ref. 4). The detailed studies of Griffith (Ref. 5) and Rebecca Lancefield (Ref. 6) took place almost 50 years later and defined the surface antigens, which allowed for the classification of streptococci. These signal works provided the basis for another half century of immunological study of the role played by the Group A streptococcus in disease. Despite the advances in physical and chemical methods that allowed for the isolation, purification and characterization of the cellular antigens of the streptococcus and the development of experimental models that enhance the theories of immune mechanisms of the nonsuppurative complications of streptococcal infections, we have not moved far in the field of immunology from Lancefield's initial observations. Her demonstration —that the heat resistant, acid extractable, alcohol soluble protein capable of inducing antibody in animals (M-protein) is the virulence factor and that type-specific protection is induced by active immunization with "M" substance or passive immunization (with type-specific antibody)—remains the sole basis for immunization with streptococcal substance to prevent streptococcal disease.

The history of major attempts to immunize humans with hemolytic streptococci dates to the 1930's when Wilson and Swift (Ref. 7) and Swift et al. (Ref. 8) attempted to reduce the symptoms and recurrences of acute rheumatic fever by injecting heat-killed streptococci and "nucleoprotein" intravenously. These studies, though considered encouraging, failed to demonstrate effectiveness in either area, but did elicit severe systemic reactions in the tested patients. Rantz et al. (Ref. 9), in 1949, immunized humans with heat-killed Group A streptococci, Types 3 and 17, inducing what was described as severe systemic toxicity. Toxicity was described as being of three varieties: (1) Systemic reactions with chills, malaise and aching, (2) swelling and soreness of the injected limb, and (3) nodule formation with no difference described for the types tested. He was able, however, to demonstrate anti-M-protein (using the Rothbard method), implying the development of type-specific immunity.

Recent immunization trials have been accomplished with isolated cell wall fractions with attempts directed at establishing antigenic purity of the M substance. Of note are the reports of Massell et al. (Ref. 10), who describe the occurrence of two cases of acute rheumatic fever and one suggestive case, following the immunization of 21 healthy siblings (ages 6 through 12) of rheumatic fever patients with a partially purified M-protein preparation of Type 3, Group A streptococci. The described attack rate of acute rheumatic fever of 11.1 percent (or 16 percent if calculations include the case of probable rheumatic fever as well as the two cases of definite rheumatic fever) is noted by the author to be in excess of the 2 percent incidence described for their control group. This description of altered responses to streptococcal M-protein injections is the first recorded suggestion of such phenomena since Swift, Hitchcock, Dereck and McEwen described postvaccinal reactions in rheumatic fever patients receiving intravenous streptococci.

This observation, however, was not reproduced in the studies of Fox et al., in which a highly purified preparation of M-protein was used to immunize human volunteers (Ref. 11). Fox has continued his careful studies without evidence of such complication while demonstrating significant immunity in infants immunized with purified T_{12} M-protein (Ref. 12). Local (delayed cutaneous erythematous) reactions with minimal induration are cited as occurring occasionally. No instances of fever, malaise, postimmunization clinical signs, or laboratory findings are reported in these studies. It should be stressed, however, that the type of experimental material used in the Fox study was very highly purified and, in this regard, bears little resemblance to the products being considered by this Panel.

The hypothesis relating the etiology of poststreptococcal complications to the cytotoxic effect of streptococcal antibody on cross-reacting antigens of heart and kidney tissue has been raised as an objection to immunization with streptococcal antigens. Kaplan and Meyesarian (Ref. 13) demonstrated cross-reactions between streptococcal cell wall protein and mammalian myocardium. Zabriskie and Friemer (Ref. 14) described fractions of the streptococcal cytoplasmic membrane that share antigenic determinants with heart muscle. Although antiheart and antikidney antibodies have been demonstrated in the sera of patients during the acute phase of poststreptococcal disease, a causal relationship between these antibodies and cytopathology has not been established.

Fox (Ref. 12) notes that no antiheart antibody has been observed in the post-immunization sera of infants or adults receiving his purified M-protein preparation.

There are no available data to determine what quantity of streptococcal antigen would be required to induce dangerous tissue reactions in humans. Therefore, the potential for danger must be considered to exist even in preparations containing small amounts of streptococcal antigen such as in those to be used for desensitization rather than immunization.

In view of the carefully conducted controlled studies currently under way with purified chemically defined antigenic preparations, one finds it difficult to justify the use of uncontrolled, poorly defined preparations presumed to contain antigens that have been demonstrated in earlier studies to produce local and systemic reactions. The hypothetical and theoretical objections stemming from laboratory studies linking mammalian and streptococcal antigens have been given serious consideration in the design and conduct of present studies treating humans with the newer purified streptococcal antigens. Equal consideration should

be extended to those being treated with mixed bacterial antigens containing Group A streptococcal products.

CONCLUSIONS AND RECOMMENDATIONS

The Panel concludes that, based on the available information, the uncontrolled use of Group A streptococcal antigens in all bacterial vaccines and bacterial antigens with no U.S. standard of potency represents unacceptable actual and theoretical risks. It therefore recommends that the Group A streptococcus and its products be removed from all vaccines and antigens represented in this group.

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LABELING

General problems of labeling of drugs used in man have been the subject of many extensive reviews. Panel members have been made aware of a draft of an FDA document on "Labeling for Prescription Drugs used in Man," which is intended for publication in the FEDERAL REGISTER. Rather than reviewing the same ground in a detailed position paper, it was felt appropriate to react to this document.

Panel members agree that: (1) The existing FDA proposal for labeling, published in the FEDERAL REGISTER of April 7, 1975 (40 FR 15392–15396), reflects its opinion and no changes are suggested.

(2) Vaccines and antigens that have been recommended for Category IIIA, i.e., licensure permitted to continue for a limited time while further studies are done, require separate considerations on labeling.

(3) The package inserts for most of these products are inadequate and outmoded and in serious need of reevaluation and revision. There is a need for long-term clinical followup with revision of the insert as indicated by experience. Continued followup data during use would allow for updating of toxicity, side effects, dosage, and extension where indicated to new use. Useful information about safety and effectiveness should be provided directly to patients who receive products continued in use. The package insert or circular used to satisfy the need for consumer information should contain the updated information provided to the prescribing physician. The package insert or circular given to the patient and physician should also state in boldface, at the beginning, that this product is under review by FDA for a limited time since safety and effectiveness have not been substantially established. In particular, it should be noted that adequately controlled human trials have not been done.

RECOMMENDED PROCEDURES FOR THE EVALUATION OF EFFECTIVENESS AND SAFETY OF SUBJECT VACCINES AND ANTIGENS IN HUMANS

1. *Introduction.* Well-designed clinical trials are necessary for the evaluation of the safety and effectiveness of any biological designed for human use. Details of recommended features of such trials can be found in many published articles and standard texts. In addition, essentials of adequate and well-controlled clinical investigations have been previously identified (21 CFR 314.111 (a)(5)(ii)). This section will review these general guidelines specifically in relation to the problems presented by the biologicals under study by this Panel. It is also presented in response to the charge to the Panel to provide recommendations to manufacturers for the type of studies required to develop acceptable evidence of safety and effectiveness.

2. *General principles*—a. *Need.* A clinical trial is deemed necessary for a product when there is no consensus among experts that its safety and effectiveness have been substantially demonstrated. The type of trial selected will be influenced by both the natural history of the disease to be treated and ethical considerations. When the natural history of the disease state is not well understood or when spontaneous fluctuations in severity are known to occur, the trial must include appropriate control groups. Such controls would be considered unethical when there is a consensus that the biological to be studied is safe and effective. A trial also would be unethical if there is a consensus that the biological to be studied is unsafe or ineffective.

It is the opinion of the Panel that the biologicals under review which have been classified in Category III meet the criteria of need for controlled trials in that the disease states for which they are intended show considerable spontaneous variation and ethical considerations do not preclude the use of controls.

b. *Prerequisites.* Extensive clinical trials logically cannot be performed each time a new lot of a given biological is prepared. If results of clinical trials of initial lots are to be extrapolated to subsequent use, there is an implicit assumption that the biological characteristics and stability of the product can be adequately controlled by the manufacturer. The Panel has noted that this prerequisite has not been adequately fulfilled by many of the products under review, and wishes to emphasize its importance. A further discussion can be found in the section of this report on "Standardization of Vaccine or Bacterial Product Content" and specific deficiencies are noted in the reviews of individual products.

c. *Planning and coordination.* A complete detailed protocol for the conduct and analysis of the trial should be prepared under the aegis of the sponsor. Results obtained from clinical trials whose protocols were not mutually agreed upon by the sponsor and the FDA will not be excluded from consideration. However, to minimize possible conflicts in the interpretation of results, the protocol should be reviewed beforehand with the FDA and be mutually acceptable.

3. *Guidelines for the protocol*—a. *Subjects.* Criteria for inclusion should be stated as specifically and unequivocally as possible. Those included should be representative of subjects for whom the product is to be recommended. The criteria should include age, signs, symptoms, laboratory findings and other factors considered to be most characteristic of the condition whose treatment is to be studied. The Panel feels that the specificity of the disease state to be studied has been a severe limiting factor of trials performed with the products under review. The term "asthma," for example, represents such a diverse set of etiologic and pathogenetic problems that a single method of biological control might not be applicable in all circumstances. Failure to narrowly define disease states may result in inconclusive trial data, even if the biological under investigation is truly beneficial for a defined subtype of the disease. When double-blind trials are planned, prospective participants must be fully informed of the procedure.

b. *Specification of treatments.* Complete descriptions of dosages, routes, schedules, durations, contingent modifications or other aspects of medical management of participants will be clearly stated in the protocol. There should be both an experimental and a control group. The Panel recognizes that specific circumstances may preclude the possibility of complete adherence to double-blind procedures. However, the placebo-controlled double-blind evaluation of responses remains the most reliable of designs. Any deviation from this design must be accompanied by an explanation of why rigid adherence is not feasible. Following a prearranged period, crossover of treatments may be desirable in some conditions. Information from the crossover period will be considered adjunctive to the results from the initial phase of treatment.

c. *Definitions of response.* The protocol should provide an unequivocal definition of an individual response, either qualitative, ranked or measurable. The Panel has noted that a lack of precise, objective definitions of responses has been a limiting feature of trials involving many of the products under review.

d. *Randomization.* The random allocation of subjects to the treatment groups should be performed using a table of random digits or other closely related methods. Alternate entry procedures are not acceptable, nor is any method by which single codes are used for experimental and control groups.

e. *Collaborative investigations.* Ideally, the trial would be conducted simultaneously under the supervision of investigators in different geographic locations. When done in this fashion, the protocol should specify the design used to assure maximum randomization of lots of vaccines and antigens, time of entry into study, age, sex, etc., so as to prevent possible imbalances between two treatment groups in one location.

f. *Records.* Complete record sets should be maintained at a central office in such a way as to assure supervision of protocol adherence and monitoring for adverse or otherwise unanticipated effects. All participants in a trial must be accounted for completely.

g. *Statistical analysis.* It is crucial to include expert biostatistical consultation on all phases of the controlled trial, particularly in its initial design and sample size deliberations. This would help minimize design defects which might complicate analysis. Levels of significance for all tests to be employed in a particular study should be mutually agreed upon in advance by the sponsor and FDA.

h. *Discovered effects.* Modified definitions, recombinations of categories, and adjustments for variables not explicitly provided for in the protocol may lead to the discovery of unanticipated effects. While the search for such additional insights is to be encouraged, they may require confirmation from additional studies before being construed to be prima facie evidence for or against effectiveness.

i. *Safety during clinical trials of effectiveness*—(1) *Subjects.* There should be careful screening to eliminate those who may be subject to adverse reactions. When feasible, all participants shall have discontinued previously administered agents for an agreed upon period before entering the trial.

(2) *Clinical observations.* Physical and laboratory observations should be recorded on entry and subsequently, at regularly prescribed intervals. The tests selected will be those considered pertinent to safety considerations of the product under trial.

(3) *Adverse events.* Two classes of adverse events can be considered—those which are anticipated as possible consequences of experimental or control treatments and those not anticipated. Anticipated events should be specified completely in the trial protocol and a detailed standard form should be developed for their recording. The relative importance of these events should be weighted prior to onset of the trial by mutual agreement between the sponsor and FDA. The relative importance of unanticipated events must be assessed by a comparison of their incidence in the experimental and control groups. As in the analysis of effectiveness, the degree of difference in rates which is considered to be significant should be agreed upon beforehand.

(4) *Continuation of trial.* New patient entries into the trial shall be suspended if the adverse events in either group are considered to be of sufficient importance as described above.

4. *Additional measures for determination of safety.* Concomitant with the authorization for general use of a bacterial vaccine or antigen, the Panel urges that a program for the surveillance of randomly sampled recipients be instituted and maintained for as long as the product remains on the market. Two basic types should be used:

a. *Short-term studies.* The basic purpose of short-term surveillance is to allow inclusion of sufficient recipients so that adverse effects which occur at relatively low rates may be detected. These rates may be too low to be discernible in the controlled trials, yet may be considered unacceptably high in relation to the potential benefits of the biologic in question.

The trials therefore would follow existing guidelines for inclusion and observation of participants, but would not require a control group. The number to be included should be determined in advance with statistical consultation and should be sufficient so that the presence or absence of an agreed upon rate of significant adverse reactions (1:500, 1:1,000 etc.) may be determined within reasonable statistical confidence limits. Duration should be as long as the customary length of treatment. Some modification will be required when courses of treatment are either intermittent (seasonal) or continuing.

Should a significantly high rate of adverse reactions be definitively encountered, it is recognized that a causal relationship may not necessarily be inferred. In such an instance, controlled trials would have to be reinstituted using a sufficiently large number of participants to provide a significant answer. A significantly high rate of adverse reactions may be defined as one which alters the benefit-to-risk ratio to the extent that use of the product is not justifiable.

b. *Long-term studies.* The basic purpose of long-term surveillance is to search for adverse effects which are demonstrable only after many years. The Panel recognizes the inherent difficulties of developing long-term prospective studies. It will be noted that the products under consideration by the Panel are not uniformly employed. Thus, there will exist at any given time, sufficiently large groups of persons of similar disease states, age, sex and socio-economic status who have never received the product in question. Incidence and/or prevalence rates of major illness indicators, including death, can then be compared in populations whose essential difference is whether or not there has been prior receipt of the product under study.

To accomplish this, a protocol should be submitted which:

(1) Details methods of obtaining a random sample of subjects;

(2) Specifies methods by which all such subjects can be traced through time so that the potential bias of unexplained loss to followup is not present;

(3) Lists the major disease states and adverse reactions which are to be studied and details the methods of surveying for these states; and

(4) Specifies the number of participants to be involved with an indication of the magnitude of the attributable risk which could be detected in that sample size.

Specific Product Review

Mixed Respiratory Bacteria Manufactured by Center Laboratories, Inc.

1. *Description*—a. *Composition.* A mixture of washed organisms killed by "gentle inspissation," suspended in physiologic saline containing 0.4 percent phenol and consisting of:

	Percent
Staphylococcus aureus, American Type Culture Collection (ATCC) 6538 DR Strain PCIR 09/D, FDA	30
Staphylococcus albus, ATCC 9491	30
Neisseria catarrhalis, ATCC 8176	10
Klebsiella pneumoniae, ATCC 9590	[1] 5
Klebsiella pneumoniae, ATCC 9591	5
Streptococcus mitis, ATCC 9811 (Sherman Strain MFA, Cornell University)	3.33
Streptococcus salivarius, ATCC 9222 (Gunsalus Strain S20B, Cornell University)	3.33
Streptococcus pyogenes, Group A, ATCC 12344	[1] 3.33
Diplococcus pneumoniae I, ATCC 6301	3.33
Diplococcus pneumoniae II, ATCC 6302	3.33
Diplococcus pneumoniae III, ATCC 6303	3.33

[1] Type I.

b. *Preparation.* The package insert states that:

[E]ach organism is grown on a medium specially formulated for the needs of that organism and with the ultimate objective of obtaining it free of any contamination with foreign antigenic materials. Each growth is harvested separately, washed, and at each step identified by microscopy and subculture so that there is no alteration in the integrity and purity of the product. The final concentrated washed organisms are then killed by gentle inspissation and suspended in physiological saline with a suitable preservative. Each suspension is counted, and the final mixture made from the counted pure, identified suspensions of the separate organisms. The final Allergenic Extract of Mixed Respiratory Bacteria is tested for sterility and safety in accordance with all the applicable regulations.

It is further stated in the package insert that:

The organisms are identified and have been in pure culture isolation and maintenance for a sufficient period of time to assure stability and purity of species and variety.

2. *Labeling*—a. *Package insert.* The package insert gives directions for use of the product as a desensitizing agent for persons "clinically reactive to the common flora of the upper respiratory tract." A suggested simple dosage schedule for subcutaneous injections is provided from strengths of 1 to 1,000 million organisms per milliliter, based on the patient's degree of sensitivity. The instructions for managing reactions are standard ones. The warning for treatment of systemic reactions and precautions to be observed in administering vaccine seems adequate.

b. *Labels.* Sample labels are given for concentrations of 1,000; 100,000; 1 million; 10 million; 100 million; and 1,000 million killed organisms per milliliter. These labels include a list of organisms instruction for storage and initial dose. The size of printing is very small and difficult to read.

3. *Analysis*—a. *Description.* The source of each organism is ATCC (American Type Culture Collection, 12301 Parklawn Drive, Rockville, MD 20852). The manufacturer does not state how the stock cultures are maintained or stored to "assure stability and purity." There is no specific information about the methods of achieving "the ultimate objective of obtaining the bacterial growth free of any contamination with foreign antigenic materials" or how it is attained or checked other than the statement "each growth is washed and at each step identified by microscopy and subculture." There is no indication of the original concentration of organisms in the individual stock culture suspension, except by inference that 1,000 million organisms per milliliter might be the strongest concentration, since this, the strongest mixture marketed, is used in the individual component animal safety test.

The statement, "The organism count is verified by counting chamber technique and opacity standard method," could be interpreted as meaning either both methods, or one or the other method is used. In testing for bacterial agglutination, the McFarland barium chloride turbidity scale is employed. Each organism is tested for antigenicity by its ability to induce agglutinating antibody in rabbit sera. The information given does not state what concentration of organism per milliliter, or what nitrogen content per milliliter is used for the inoculum, since only the volume of suspension is stated. No antibody titers are provided following this immunization program. "If the antibody titer is adequate and serologically specific for each respective organism, each animal is then exsanguinated, the serum separated, and stored for future use, frozen and/or freeze dried."

The manufacturer does not state how he uses the information obtained by rabbit immunization or by slide agglutination with these antisera to select organisms or batches of organisms for his individual stock vaccines or for the final mixed product.

b. *Labeling.* The size of printing on the label is so small that it is difficult to read. The rationales for the selection and percentages of each species used in the vaccine are not provided.

The insert is plainly worded and informative but makes the unsubstantiated claims for desensitization of individuals clinically reactive to the common bacterial flora of the upper respiratory tract. No specific disease entities or details of what constitutes "clinically reactive" are mentioned. There is no claim for its use as a preventive for respiratory infections. The dosage is to be based on "patient's degree of sensitivity," but no suggestions are made as to how this sensitivity is to be determined by the prescriber. The statement regarding local reactions is ambiguous. "Swelling (Edema), redness (erythema) and pain at the site of injection in 10 to 30 minutes are characteristic. The dose for subsequent treatment should be reduced to the previous dose which elicited no local response or the dose eliciting a response should be repeated."

c. *Effectiveness.* The respiratory bacterial vaccines have been used in attempts to (1) stimulate immunity and (2) diminish, or desensitize to, bacterial allergy. Since the manufacturer indicates this vaccine is to be used as a desensitizing agent, one would expect to find evidence presented for this process in sensitive humans or experimental animals, pursuant to the "Recommended Procedures for the Evaluation of Effectiveness and Safety of Subject Vaccines and Antigens in Humans" in this review, and § 314.111(a)(5)(ii) of the regulations (21 CFR 314.111(a)(5)(ii).

The manufacturer presents no specific studies of the effectiveness of this particular vaccine. The references cited for animal studies are those of Eisen and Bacal (Ref. 1 below), who report the development of circulating antibody to the polysaccharide antigens of staphylococci, pneumococci and Rantz antigen in children and rabbits. Immunized guinea pigs had skin reactions to staphylococci and streptococci. Two papers describe the induction of interferon in mice by bacterial vaccines (Refs. 2 and 3), but since this submission, unsuccessful attempts to confirm the induction of interferon by this product in humans have been reported (Refs. 4 and 5).

The series of 17 papers listed by the producer, report uncontrolled human studies on effectiveness and do not deal with the product under consideration. They include many of the same reports that are frequently quoted to support the efficacy of all the mixed bacterial vaccines in this group. Tuft and Ermilio (Ref. 6) report a reduction of 70 percent in the frequency of asthma and/or rhinitis, after the intracutaneous administration of a bacterial vaccine containing *Staphylococcus aureus,* pneumococcus, *H. influenzae, Neisseria flava, Streptococcus viridans* and other hemolytic and nonhemolytic streptococci. Moore and Reed (Ref. 7) questioned the significance of their own uncontrolled study of stock and autogenous vaccines, which gave 50 to 75 percent improvement, in the absence of double-blind placebo controls.

Among the controlled studies attempted, those of Barr et al. (Ref. 8), Mueller and Lanz (Ref. 9), are quoted as showing effectiveness of bacterial vaccines in asthmatic adults and children, respectively. Both studies have certain characteristics in their statistical designs, which detract from the forcefulness of their conclusions on effectiveness.

d. *Potency standards.* These are outlined in the general statement of the Panel on product standards and potency which, for this product, specifically include the conditions that:

(1) The biologically active ingredients said to be present in a vaccine must be enumerated.

(2) Methods for detecting and measuring each identifiable ingredient must be provided.

(3) Methods for the estimation of the biological activity of each ingredient, both individually and in combination, under suitably controlled conditions must be provided.

e. *Safety.* Quoting from the Panel statement on Drug Safety, Safety as it relates to bacterial vaccines and bacterial products, indicates freedom from harmful effects on persons, directly or indirectly. Biologic products, by their nature, however, must be considered to have a potential for danger.

The product must be sterile, pure, free of harmful additives and constituents, and remain stable under recommended conditions of storage and use. It should be shown to be safe and free of undesirable and adverse side effects by adequately controlled clinical trials, as well as in preliminary well-designed animal experiments, both for acute and chronic toxicity.

The bacterial vaccines in long use that have been reviewed by this Panel, including this product, have not been subjected to such rigorous criteria in their many years of clinical usage. Other than tests for sterility, some monitoring of

certain vaccines for pyrogens, the absence of deliberate additions of any previously recognized harmful ingredient and the apparent absence of ill effects during many millions of injections, there has been no systematic examination of the safety of these vaccines.

Theoretically, the polysaccharides of pneumococci and *H. influenzae*, and various media constituents could produce long-term adverse effects, but presumably the rate is very low. The Panel has concluded that Group A streptococcal products carry undesirable long-term risks and therefore should be removed from all vaccines.

The evidence for animal safety presented is confined to the general safety test for the 7-days survival of two mice and two guinea pigs, as described in Part 610—General Biological Products Standards (21 CFR Part 610), and specifically in § 610.11 (21 CFR 610.11). The manufacturer presents no studies specifically related to the safety of this particular vaccine. Human safety is addressed in the submission by references to two texts on the practice of pharmacy (Ref. 10) and bacteriology (Ref. 11), which include the use of killed bacterial vaccines for immunization. The submission refers to Willis' (Ref. 12) study of 500 rheumatic patients treated with a heat-killed polyvalent streptococcal and staphylococcal product. "There was temporary aggravation of joint pain but in not a single instance were effects observed attributable to the vaccine, while the ideal dosage was being determined." There are no references to Massell's recent studies (Ref. 13) with purified M-protein vaccines of streptococci, during which reactions were noted.

Consideration is given to several references cited (Refs. 14 through 17) on the local or systemic reactions that may occur after the injection of vaccine; none are said to have been significant or severe.

Marketing experiences in which no adverse reactions were reported to the manufacturer in 1971 and 1972, are cited in support of the safety of this product.

No analyses of clinical case reports are included in the presentation.

f. Benefit-risk consideration. No specific conditions for the use of this product are cited. The desensitization of persons sensitive to bacteria of the respiratory tract can encompass a variety of clinical conditions. The inference is that the vaccine will be used chiefly in asthma related to respiratory infection. This implies the existence of a subpopulation that reacts in a peculiar fashion to bacterial infections. This population needs to be more clearly identified and monitored for both good or bad effects of the use of vaccine to be estimated.

The risk of immediate catastrophic reactions to mixed bacterial vaccine might be assumed to be very low, in view of the many years of clinical use of various vaccines, and the paucity of such reports in the literature. Adverse reactions have not been reported to the manufacturer in marketing experience in 1971 and 1972 according to this submission. The possibility of the risks of late or mild reactions to bacterial products have been noted and discussed by the Panel. These possibilities are not dealt with in this submission.

4. *Conclusions*—a. *Critique.* The entire presentation is sketchy, particularly in the details relating to the actual composition of the product and its method of manufacture. There is meager information regarding potency, the serologic tests described and how they apply to the standardization of the vaccine. There are no studies directly related to the safety or effectiveness of this particular combination of bacterial vaccines, in either animals or humans. The literature cited as supporting its safety and effectiveness is meager and, in fact, concerns preparations having similar bacterial content, but containing heat or chemically killed organisms. It includes other aspects such as immunization and interferon production; as well as desensitization.

b. *Recommendations.* It is recommended that this product be placed in Category IIIB and that the appropriate product license(s) be revoked for the following reasons:

(1) There is no substantial evidence of safety or effectiveness.

(2) There is no evidence presumptive of safety. The evidence cited from the literature by the manufacturer refers to other similar combinations of bacterial species and thus does not apply in particular to the combinations under consideration.

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STAPHAGE LYSATE (SPL) FOR STAPHYLOCOCCAL DISEASE MANUFACTURED BY DELMONT LABORATORIES, INC.

Smith (Ref. 1 below), in a recent review, stated that between 1900 and 1904, Wright coined the term "autogenous vaccine" and introduced autogenous vaccines into the treatment of patients with chronic or recurrent infections. Smith describes the results obtained by investigators other than Wright as inconsistent, ranging from patients who appeared to undergo some harm, to others in whom the disease was unaltered, to some who seemed to have had dramatic responses.

Wright utilized a typhoid vaccine consisting of killed bacilli whose administration was followed by agglutinin formation. Later, he measured responses with an opsonocytophagic test, which he had developed. From typhoid vaccine, he went on to treat patients suffering from recurrent boils over a period of months to years with a vaccine made from heat-killed homologous staphylococci isolated from the individual. He reported that as the opsonic index improved following increasing doses of the vaccine, the patient's boils tended to disappear. While small "stimulating doses" of the vaccine seemed to improve the rate of phagocytosis, this was not always readily accomplished because some vaccine doses produced either local or systemic reactions, or both.

The use of autogenous vaccines in the treatment of asthma was initiated as early as 1910 by Sicard (Ref. 2). By 1920, Rackemann (Ref. 3) had begun to treat such patients with autogenous vaccines prepared from heat-killed organisms that had been isolated from their sputa. He used skin tests to demonstrate hypersensitivity and subsequently concluded that the vaccine acted through "desensitization" of the patient to his bacterial flora.

During the following 20 years, arguments and interest waxed and waned over the use of staphylococcal and "respiratory bacterial" vaccines. A decrease in their popularity followed the appearance of sulfonamides and antibiotics. When penicillin resistance in staphylococci became a problem in the late 1950's and early 1960's, there was a resurgence of interest in other forms of therapy, but vaccines did not achieve great popularity, probably because many of the problem illnesses were acute and not suited to an agent that required long-term administration.

Recently, as interest in cell-mediated immunity has come to the fore, Mudd and others have proposed that repeated injections of staphylococcal vaccines in the experimental animal suppress the reactivity of its leucocytes to the injected antigens.

In another direction, Twort in 1915 and d'Herelle somewhat earlier, independently discovered a transmissible lytic effect on bacteria (bacteriophage), which became known as the Twort-d'Herelle phenomenon. Since living bacteria were lysed in vitro, it was only natural for bacteriophage to become attractive as a potential therapeutic agent. Consequently, phage was used in the living host as well as for the preparation of material for immunization. Eaton and Bayne-Jones extensively reviewed (Ref. 4) the subject of bacteriophage therapy and concluded that "The favorable reports may have been due to the specific immunizing action of bacterial proteins in the material used and to nonspecific effects of the broth filtrates." They also summarized a report by Larkum, who had treated patients with furunculosis by injecting 2.0 milliliters of bacteriophage subcutaneously on 2 successive days. Among 208 patients who received such treatment, 60 had no reactions, 72 had mild responses, 15 had general responses, and 2 had severe reactions. No information on reactions was obtained from the remainder. Larkum also stated that 78 percent of his patients had no recurrences in the 6-month period following treatment. Only 3 percent were unimproved, and the remainder had recurrences of varying degrees. Thirteen of the "cured" patients had previously failed to respond to autogenous vaccines. Only 2 of 23 acne patients were "cured" by phage injections.

The Eaton, Bayne-Jones review concludes that,

> While bacteriophage dissolved sensitive bacteria in cultures and causes numerous modifications of the organisms, its lytic action in the body is inhibited or greatly impeded by blood and other body fluids.

With the interest in acute and chronic staphylococcal infections on the part of both physicians and patients during an era when no suitable chemical or antibiotic therapy was available, attempts were made to either induce or to bolster the defenses of the host. Apparently, Staphage Lysate (SPL) was an outgrowth of this search.

1. *Description.* According to the submission, The product is an ultrafiltrate of the complete bacteriophage lysate (Gratia polyvalent bacteriophage) of appropriate specific propagating strains (parent cultures) of *Staphylococcus aureus* (Cowan Serological Types I and III).

It is further stated that:

> Bacteriological sterility is achieved by use of excess bacteriophage and ultrafiltration (0.02 Seias filter candles) and maintained by meticulous aseptic technique.

The finished product consists of the following:

a. A full representation of the antigenic components of the entire staphylococcal cell ($1.2–1.8\times10^8$ colony-forming units/ml) rendered soluble by the lytic process, the metabolites and the heat labile and heat stable intra- and extra-cellular enzymes elaborated by *S. aureus;*

b. Active bacteriophage ($1\times10^5–1\times10^9$ plaque-forming units/ml);

c. Ingredients of the culture medium (Bacto, heart infusion broth, dehydrated, Difco).

2. *Labeling.* SPL is marketed as two products, each labeled Bacterial Antigen. One (white label) states that it is made from *Staphylococcus aureus,* Serologic Type I and is for aerosol, topical and oral use only. For aerosol usage the dosage range is 0.1 to 1.0 milliliter, for topical usage the dosage range is 0.25 to 2.0 milliliters, and for oral usage the dosage range is 1.0 to 2.0 milliliters. The label includes a lot number, expiration date, and instructions to store the product at 5°C (±3°C). The product contains no preservative and is not to be used if it becomes cloudy. Each package contains 10 milliliters.

There are two package types for the second preparation, SPL–Types I and III. One is the same as for SPL–I, described in the preceding paragraph, and the other contains similar statements on its label (yellow), except that it is for subcutaneous and aerosol usage. For subcutaneous usage the dosage range is 0.05 to 0.5 milliliter and for aerosol usage the dosage range is 0.1 to 1.0 milliliter. A package consists of ten 1-milliliter ampules, each containing equal parts of Types I and III staphylococci. It too has no preservative, and the user is cautioned to employ "a separate heat-sterilized syringe and needle for each patient" and not to use the product should it appear cloudy.

3. *Analysis*—a. *Animal safety data.* Each lot is tested prior to its release in accordance with FDA regulations. It is stated that,

> during the course of routine testing of 280 lots over a period of 15 years (never) has any evidence of significant unfavorable symptoms or deaths of 1,120 test animals resulting from the administration of SPL has been observed.

From time to time, other nonroutine tests have been conducted. These have included two intravenous doses of 25 milliliters each to three grown chinchilla rabbits at 7-day intervals, with none ever becoming ill. Whenever such rabbits were retested after a 12-week period with 3 milliliters per kilogram intravenously, none showed any evidence of hypersensitivity.

b. *Human safety data.* This is based upon correspondence with individual physicians and reports in the literature (Refs. 15 and 17). In addition, the submission states that millions of doses have been administered and that there have been "no complaints of prohibitively undesirable side effects resulting from SPL administration, when used as directed."

c. *Effectiveness data.* The following data were submitted by the manufacturer regarding the finished biological product.

(1) Controlled studies (Ref. 15).

(2) Partially controlled or uncontrolled.

(3) Documented case reports of individual patients submitted by their physicians.

(4) Pertinent marketing experiences that may influence a determination as to the effectiveness of the finished biological product. Representative letters from physicians were included with the submission.

The producer "has never made a practice of journal advertising or direct mail advertising." SPL is promoted only by providing physicians who prescribe it or those who inquire, with "documented results of current studies relevant to SPL which appear in learned medical and scientific journals along with clinical notes (case reports) and periodic information letters." Presumably, this is the method that has been used to estimate effectiveness and to transmit this information to the physician. Copies of some reports from journals were provided in the submission. One of the more recent papers states that if mice were injected repeatedly with staphylococci and if they were then "elicited" by SPL, the mice were subsequently more resistant to influenza virus (Ref. 5).

Mills (Ref. 18) described his experiences beginning in 1946 with SPL-like material administered by nasal aerosol as a supplement to other treatments of sinusitis. The author discusses 60 cases of chronic sinusitis, which "constitute a random sampling of patients who had proven stubborn to conventional treatment." When he combined the "excellent" and "good" responders, 78 percent fell into this combination. These response categories are not defined nor was any attempt made to achieve randomization or "blindness." This is in essence an anecdotal report, which does not lend itself to objective analysis.

Baker (Ref. 15) described a 4-year study of staphylococcus phage lysate aerosol therapy in chronic asthma. The 50 patients studied were selected from a group of 150 receiving intranasal and intrabronchial treatment with SPL aerosol, and 40 were selected on the basis of:

(i) Those who had received adequate allergic therapy for 5 months or more with little or no benefit;

(ii) Those who had had bronchial asthma long enough so that the course of their symptoms was steady and constant;

(iii) Those whose nasal and nasopharyngeal repeated cultures revealed

the presence of pathogenic staphylococci;

(iv) Those without other systemic disease that could confuse the asthmatic picture.

Twenty patients were selected as controls and were given aerosol-containing culture medium. The basis for selecting the controls was not defined.

The treated (experimental) group received SPL intranasally after clearance of the airway by irrigation with "isotonic dextrose or physiologic saline." Vasoconstrictor nose drops were described as being used to clear the nares of excessive mucus. SPL-designated Type I and Type III were described as being available, but Type III, for reasons not explained, gave rise to "flare ups" of asthmatic symptoms, and its use was discontinued.

The Type I Lysate was rendered according to the following schedule:

Dose number and interval	Lysate	Dosage volume (milliliter)	Site of application
1 to 6, q 1 to 4 days	Type I	0.1 to 0.2	Intranasal.
7 to 12, q 2 to 7 days	do	0.2 to 0.5	Do.
13 to 22, q 4 to 7 days	do	0.2 to 1.0	Intranasal and intrabronchial.

The controls were described as having no improvement or reaction during the first 6 weeks of the study. At the end of 6 weeks the control group was started on SPL.

The authors described definite improvement in all patients, although improvement was described in some instances during the first six treatments, with continued improvement thereafter. No compilation of treatment results was described for the 6-week period during the controlled portion of the study.

Results were described as, 44 percent (22 patients) "excellent," 42 percent (21 patients) "good" and 14 percent (7 patients) "fair." This study cannot be considered a controlled study, but if the observations are accurate that status asthmaticus attacks were prevented in a group described as severe asthmatics, some degree of effect may be inferred.

Reactions were noted only in the early stages of treatment and were described as mild. The discarding of a batch of test material because of reactions is noted and implies a potential for other reactions.

As regards the studies of Salmon and Symonds (Ref. 17), the Panel notes that patients are said to have recovered because of antibody induction but no data demonstrating such responses are provided. Cases were treated over a 7-year period, 1954–1961.

Boger et al. (Ref. 6) described an attempt to control staphylococcal skin infections among institutionalized mentally retarded individuals. Although the authors, at one point, tried to control their studies, the description of the procedure devised for this purpose is incomplete. Their previous trials were essentially anecdotal and limited to the "worst" cases. The "controlled" series was indecisive. There was no discernible difference in the results in the two groups (16 persons each), but the total level of skin infections had decreased. Boger in his discussion states,

> Of some interest is the fact that some lots of the bacteriophage-lysed vaccine and certain commercially available toxoids have not given significant rises of antibody titers as measured by the Boger-Frankel-Gavin test.

Whatever the merits of this antibody system, this experience may point to some differences in lot potency of shelf-life resistance.

Bryant et al. (Ref. 7) described a randomized double-blind trial in which SPL prepared by Delmont Laboratories was used as the vaccine. The controls received broth used to produce the vaccine. The subjects were children 6 to 12 years of age, living in an institution under good hygienic conditions. No differences were noted between the effects of either the vaccine or placebo on the occurrence of furunculosis.

Some information sheets sent to physicians by the manufacturer contain brief case reprts, sometimes with conflicting conclusions. One, dated July 1971, ends with "In line with this new concept of cell-mediated immunity the use of SPL as a specific eliciting agent is making significant advances." In another clinical note, dated February 1972, after describing the case of a 6-year-old child with bronchial asthma, there is the statement, "Injections have been shown to be the best method to maintain immunity to staphylococci." In a following note, after a lengthy discussion about how SPL may be "altering the macrophage of the patient, that is converting cellular allergy to cellular immunity," there is the statement that,

> Clinical observations reported to this laboratory by physicians over the past 15 years in which SPL has been found to be effective in reducing the number and severity of upper-respiratory infections, add to the mounting evidence in support of nonspecific cellular immunity.

The individual case report forms, which constitute the major share of this portion of the submission, record brief, uncontrolled observations that usually include a general diagnosis, little or no evidence for a staphylococcal origin of the problem, some indication of the route of administration, but often not of dosage, and end with a checkmark alongside of "excellent" to indicate the degree of clinical response.

More recent publications, which date from about 1970, are concerned with the question of delayed-type hypersensitivity. "Delayed-Type Hypersensitivity to *Staphylococcus aureus* in Human Subjects" (Ref. 8) is a brief report of observations in 52 patients "predominantly suffering from recurrent sinusitis, bronchitis and asthma, recurrent secondary infection in atopic eczema, or furunculosis." Patients receiving other forms of hyposensitization treatment were continued unchanged. Each of the 52 received an intracutaneous injection of 0.1 milliliter of SPL once weekly for 6 weeks. These skin tests were read at ½-hour, 3, 12, 24 and 48 hours after each injection. The first three tests produced marked immediate reactions (within 30 minutes), which subsided within 3 hours, recurred at 12 hours, and reached a maximum at 12 to 24 hours. The average diameter of the erythematous reaction decreased after 3 weeks. The authors concluded that the decrease in skin reaction resulted from hyposensitization and that such hyposensitization was accompanied by "activation of the reticuloendothelial system and with increased capacity of the macrophages to inactivate intracellular agents." Discussion of these findings stated that the authors are "well aware that presentation of the above data does not constitute acceptable evidence of clinical efficacy."

Mudd (Ref. 9) stated that the assumption that circulating antibodies protect against staphylococcal infections was incorrect. He hypothesized that most humans, as the result of frequent infections, have delayed hypersensitivity to *Staphylococcus aureus* and that cell-mediated immunity can be "elicited" by staphylococcal antigens such as SPL. No data dealing with this material or staphylococcal infections are presented.

Other papers by Mudd and colleagues, which were provided in the submission, describe studies in rabbits and mice. It is pointed out that rabbits, as the result of infections, develop delayed-type hypersensitivity to staphylococci. Also, the staphylococcal killing capacities of macrophages were increased statistically when given SPL intra- or subcutaneously in 0.1 to 0.2 milliliter amounts.

Subsequently, Mudd reported that mice hypersensitivite to *Staphylococcus aureus* and treated with SPL had increased resistance to vaccinia and influenza virus infections. In mice, also, it was found that the ability of their leukocytes to kill staphylococci was enhanced by treatment with SPL. From this and other reports, it was concluded that (SPL) specifically activated macrophage are "nonspecific in their capacity to inactivate intracellular disease agents" (Ref. 16). However, these authors do not take into consideration the possible role of cross-reactivity between taxonomically unrelated bacteria and other antigens.

d. *Labeling.* Five routes of administration are listed, but either single or multiple methods may be called for "in the treatment of staphylococcal infection and disease." Further it is stated that:

> SPL is indicated in all primary and secondary staphylococcal infections involving the sino-respiratory tract, skin, mucous membranes, wounds, burns, grafts and gastrointestinal system.
>
> SPL is indicated for the staphylococcal components of those mixed infections in which the "SYNERGISTIC" factor is causing increasingly severe problems.
>
> SPL is especially indicated for deep-seated infections such as staphylococcal septicemias, intractable osteomyelitis, severe pustular acne, chronic recurrent furunculosis and sinusitis.

SPL affords a specific therapy for staphylococcus infections, and may be used safely for the prophylaxis and control of staphylococcal disease without the hazards of hypersensitivity or toxic reactions.

In addition, "SPL Types I and III cover more than 90 percent of all strains (staphylococcal)." This includes phage types 80/81, 54 and other antibiotic-resistant strains.

SPL is a standardized product. Each milliliter contains:

(a) 2,000 million lysed, antigenically potent *Staphylococcus aureus*, antigenic Types I and III, as a whole culture antigen in solution, and

(b) more than 10,000 million active Staphylococcus bacterial phage particles.

Accordingly, SPL provides (1) a potent antigen which stimulates high antibody response in the host, and (2) the bacteriophage that destroys the infecting organism on contact.

Children receiving the vaccine subcutaneously should receive one-half the adult dose. When other routes, e.g., aerosol, topical, or oral are employed, dosages for adults and children are the same. For infants, nose drops or oral doses are the preferred routes. One should also treat acute infections with more frequent administrations than for subacute or chronic cases.

When the subcutaneous route is used, it is recommended that supplementary doses should be administered topically either by spray, pack, or installation, if open lesions or wounds are present. In gastrointestinal infections, oral doses of 1 to 2 milliliters are given every 12 to 24 hours.

The best dosage schedule is the one which produces the desired therapeutic results without causing either systemic or excessive local reactions. After reaching top or optimum dose, that dose (the maintenance dose) is repeated at 1- to 4-week intervals. Tolerance: The maximum quantity of SPL that can be given without producing general, vaccine-like reactions (malaise, increase in temperature); or an excessive local reaction (redness greater than 2 inches in diameter or uncomfortable soreness).

Administered as suggested, SPL is nontoxic, nonsensitizing, nonirritating to any body tissue or fluid. No reported anaphylactic reactions.

The package insert, dated April 1972, contains essentially the same material, except that it is expanded and lists 14 bibliographical references. In discussing the rationale for using SPL, the statement is made that although for a long time it was thought that it functioned primarily to induce antibacterial antibodies, this is not supported by modern clinical and laboratory studies.

Benefit from staphylococcal vaccines and equivalent staphylococcal products is now coming to be understood as resulting from favorable effect upon the state of cellular sensitivity to Staphylococcus.

It is further stated that repeated treatment with SPL markedly reduces cellular hypersensitivity to *Staphylococcus aureus*. The several references submitted to support this conclusion are described in the insert as "still uncontrolled." The additional point is made that SPL contains active polyvalent bacteriophage, which is able "to lyse in vitro a significant proportion of the field strains of staphylococcus, in particular the notorious hospital strains." No preservatives are added to SPL in order "to maintain maximum antigenic potency and phage activity."

Aerosols or nose drops of Staphage Lysate are the classic methods to induce a specific local and systemic immunity to staphylococci by lysis and rapid absorption of the antigen in the anterior nares, the main reservoir of pathogenic staphylococci. Intranasal aerosol inhalations allow direct access to the sinuses, throat and bronchial tubes; combined with subcutaneous injections better clinical results are obtained.

This is followed by a description as to how the aerosols should be administered. Inhalations may be repeated at 1- to 3-day intervals with increasing doses to a maximum of 0.5 to 1 milliliter, depending upon urgency and tolerance. For better coverage, one is advised to combine this with subcutaneous injections and oral doses. SPL may also be given by nose drops at home, between visits, to reduce the dissemination of the offending staphylococci from the anterior nares. Sterile droppers should be obtained for this purpose. When drops are instilled, the droppers should not touch the nose "or anything else." Those with allergies should be started on SPL Type I by aerosol and when a plateau has been reached, Types I and III may be tried.

Oral administration is rceommended for the specific treatment of staphylococcal enterocolitis. This may be reinforced by either concurrent subcutaneous injections or nose drops or both. Accessible lesions (skin, mucous membranes, eye, ear, burns, sinus tracts and ulcers) can be treated by topical applications of SPL I and III as sprays, drops, packs, or irrigations.

Under "Precautions" there is a statement that,

In common with all antigens employed to stimulate the production of antibodies that are protective in the event of subsequent disease, SPL presents the remote potential of host sensitization to staphylococcal or bovine protein. No instances of anaphylactic shock have been observed in many thousands of injections or aerosols, but the physician must bear this possibility in mind, be prepared to deal with such an emergency by having at hand epinephrine, intravenous antihistamines and corticosteriods.

The patients said to be likeliest to have reactions to SPL Type III are those "with bronchial asthma, pulmonary fibrosis and emphysema, bronchiectasis and multiple allergies * * *." In such patients, SPL presumably should not be administered by inhalation, but the other routes should be satisfactory.

To prevent relapses, it is recommended that booster treatments be provided every 2- to 4-weeks indefinitely, either by injections, aerosols, or nose drops.

4. *Conclusions*—a. *Critique*. What began as a vaccine designed to induce antibodies against staphylococci in acute, subacute or chronic infections or "allergy" to the organism, has evolved as the "medical rationale for use of Staphage Lysate (SPL) is based on the following summarized principles," (from section VII of the Delmont data submission to Panel). The ability of macrophages to destroy intracellular organisms may be increased by the processes of "induction and elicitation of reticuloendothelial function." "Induction" follows colonization or infection by *Staphylococcus aureus* and leads to delayed-type hypersensitivity, while "elicitation is achieved by administering staphylococcal antigens present in Staphage Lysate." The latter leads to a reduction in cellular hypersensitivity (desensitization) which, in turn, provides clinical benefits. The application of these principles offers "great promise in cases in which the capacity of macrophages to deal with intracellular agents is critical."

At the same time, it is emphasized that SPL contains active polyvalent bacteriophage, which in vitro can lyse different kinds of staphylococci. The statement concludes:

With a view to conforming to appropriate labeling of SPL, the package circular clearly states that SPL is distributed for the treatment of staphylococcal infections.

The package insert, while describing a number of disease variants and purposes for which SPL treatment could be used, has moved into the use of current immunologic terminology without adding any more information than was available in the past.

It is also significant that while it is stated that this vaccine contains live polyvalent bacteriophage at the time of production and following final filtration, no data are provided as to its persistence in the package during storage, or at the expiration date. It is stressed that the bacteriophage in SPL offers additional therapeutic benefits, but this is not supported by the data. Nor is there information as to whether the contained phage is antigenic in humans or animals. The recent concern about bacteriophage in live virus vaccines (Ref. 13) must be considered in reviewing this product. (See discussion on phage in statement on safety.) If live phage is present then the concern about harm to humans either in the transmission of genetic material capable of producing cancer and/or degenerative disease (Ref. 14) is valid and must be considered.

The fact that bacteriophage can replicate in certain mammalian cells (Ref. 13) as well as alter nonpathogenic bacteria to pathogens by inducing toxin production are additional factors to be considered in the evaluation of the product's safety. That bacteriophages are potent antigens in humans has been shown by Uhr (Ref. 10) in newborn premature infants. The ϕX174 bacteriophage has subsequently been studied by Ochs, Davis and Wedgwood (Ref. 11) in patients with immunodeficiency diseases. Wedgwood and Uhr did not see any adverse effects from phage. Klein-schmidt, Douthart and Murphy (Ref. 12) have reported that T4 coliphage may induce interferon formation.

The emphasis on bacteriophage appears to be unrelated to the producer's attempt to ascribe the benefits of SPL to the "elicitation" of cell-mediated immunity. While the resultant "angry macrophages" may require specific stimuli, their presumed beneficial functions are said to be nonspecific, suggesting to the manufacturer a potential new avenue for the use of this product.

Taken as a whole, the data cited above indicate the following:

(1) The evidence for this product's safety is incomplete. Since bacteriophage genetic material has been reported to enter mammalian cells and their genetic components under certain conditions, the safety of bacteriophage per se and especially in parenterally administered biologicals, is a matter of concern, e.g., witness the case of live virus vaccines (Ref. 13). SPL presents an analogous problem;

(2) This product is said to contain not only all components of the lysed staphylococcal cell, its metabolites and enzymes, but also "ingredients of the culture medium." The latter would include beef heart infusion, which may induce antibodies that cross-react with human heart muscle. No data are supplied that the vaccine's content of heart infusion broth is safe and nonsensitizing to patients of all age groups, especially when delivered to mucous membranes. In the absence of evidence to the contrary for this and the other product components, conclusions as to the safety of SPL must be held in abeyance;

(3) No objective, controlled data are supplied that demonstrate that SPL is effective in the treatment of staphylococcal infections and the other listed conditions;

(4) The suggested indications for the use of SPL are diffuse, ill-defined, and have undergone changes over the years so as to now include a new set of unsubstantiated (in man) modes of action and indications for usage;

(5) No justification is supplied for the selection of the various routes of administration;

(6) No evidence is provided that there is live bacteriophage available at the time when the material is used and that, if present, it provides any therapeutic benefits;

(7) No evidence is provided that the bacteriophage, if present, is antigenic in man and if it is, that such antibodies affect "therapeutic" activity.

b. *Recommendations.* It is recommended that this product be placed in Category IIIB and that the appropriate license(s) be revoked for the following reasons:

(1) There is no substantial evidence of safety or effectiveness.

(2) There is no evidence presumptive of safety.

(3) If SPL is to be recommended for use as a stimulator of cell-mediated immunity, either specific or general, this "new" function requires evaluation as a new biological.

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BACTERIAL VACCINE MADE FROM PNEUMOCOCCI, STREPTOCOCCI, H. INFLUENZAE, AND N. CATARRHALIS (ENTORAL) (V–404, V–408) MANUFACTURED BY ELI LILLY AND CO.

During the two decades following the influenza pandemic of 1919, extensive efforts were made to develop effective vaccine against serious infections from various bacterial respiratory pathogens. These efforts were extended to include preventive treatment of the milder recurrent bacterial complications of the common cold. Because of the impression that any vaccine effect would be short-lived and that frequent injections would be costly, time consuming and not likely to be generally accepted by patients, research on oral vaccines was instituted in animals, and results were promising. In addition to inducing antibody production, vaccines had protective effects under certain conditions. In one of the last studies reported, ENTORAL protected rats from fatal doses of pneumococcus Type I. The recommended human dose was used (Ref. 1 below).

Proponents of oral "cold" vaccines recognized the problem of developing a polyvalent vaccine that would impart immunity to the numerous species of bacteria that might complicate respiratory viral infection. Rockwell and Van-Kirk attempted to circumvent this problem by selecting organisms with high contents of heterophile antigens, on the basis that they might stimulate much broader immunity than would species-specific antigens (Ref. 2). They observed that heterophile antibody production could be induced by oral vaccine and reported some correlation between antibody titer and clinical improvement (Ref. 3). Apparently their selection of organisms for heterophile antigen was the basis for the formulation of ENTORAL (Ref. 4), though this is not explicitly stated in the literature.

1. *Description.* ENTORAL is an oral vaccine prepared in capsules. Each capsule contains the following heat-killed organisms:

	Billions
D. pneumoniae (types 1, 2, 5, 7)	40.0
Streptococcus—3 strains, (Beta-group C, untypable alpha and gamma)	15.0
H. influenzae—2 strains	2.5
N. catarrhalis—2 strains	2.5

The package label indicates that the vaccine "may be useful for increasing resistance to bacterial respiratory infections." The recommended dose for older children and adults is one capsule daily for 1 week, then twice weekly for the duration of the "infection season."

2. *Analysis*—a. *Effectiveness.* Several reports were submitted by the company which indicated that oral vaccine can induce antibody production and animal protection. The contents encouraged some clinical studies in the 1930's. Yet, even a predictable antibody response in man cannot stand as adequate proof of effectiveness unless it correlates well with a significant clinical component in an adequately controlled study. This would apply to any antibody but particularly to heterophile antibody, which has no known direct protective effect. The association of heterophile immunity and "cold" protection (Ref. 3) was found as part of a study that was not controlled adequately. In fact, though the favorable reports used control subjects, the

controls were untreated. Volunteers would be treated, while nonvolunteers served as controls.

As it turned out, the potential value of oral vaccine as a method of reducing absenteeism in schools and industry attracted the attention of physicians who were prepared to carry out double-blind, placebo-controlled studies. Two of these, one reported in 1938 and one in 1943, showed no significant benefits from oral vaccine treatment. The first study, by Diehl, Baker and Cowan, included information on the frequency of "colds" in University of Minnesota students who reported from memory, for the year preceding treatment (Ref. 5). Both the treatment and control groups had reductions of 70 percent in the average number of "colds" per person during the treatment period, compared with the preceding year—a response rate similar to that of treated groups in the earlier favorable studies. There was no difference in the number of days per person lost from school. The source of the vaccine used was not given. The number of organisms per capsule differed somewhat from ENTORAL as it is now marketed:

	Billions
D. pneumoniae (types not given)	25
Streptococci	15
H. influenzae	5
N. catarrhalis	5

The 1943 study involved 253 employees of the Henry Street Visiting Nurse Service in New York City. The vaccine capsules contained the same number of organisms as was used in the Minnesota study, and both vaccine and placebo were provided by the Eli Lilly and Company. The number of colds per person-period was similar in the treated (2.1) and control (2.2) groups. Although the number of days absent from work was somewhat less in the treated group (3.1 vs. 4.2), the authors concluded that treatment "appeared to have no influence" either on the incidence or severity of the common cold or on the secondary complications (Ref. 6).

A third study from England, also reported in 1938 and involving 1,062 workers, compared ENTORAL (composition not stated) with ultraviolet lamp treatment, vitamins A and D, lysed bacterial vaccine, and an untreated group. The study involved the number and duration of colds and working days lost (Ref. 7). Only the effect of ultraviolet treatment seemed to be better than no treatment at all.

The literature on oral bacterial vaccine, then, reflects the classical pattern, namely, an initial surge of favorable reports leading eventually to controlled studies that do not support claims for effectiveness.

In addition to the medical literature and other material submitted by the manufacturer, the Panel gave careful consideration to letters submitted to the Bureau of Biologics by users of the vaccine, who attested to its effectiveness. Unfortunately, such individual reports do not provide evidence for effctiveness in settings where high placebo-response rates exist.

b. *Safety.* There is no evidence that this product is not safe. The organisms used may be found in the nasopharynx in the absence of disease. No animal safety data were submitted by the manufacturer, and no mention of toxicity appears in reports on the biological effects of the product in animals (e.g., Ref. 1). Diehl et al. found that about 3 percent of their ENTORAL-treated subjects developed side effects, of which about half were gastrointestinal, compared with about 0.5 percent of the controls (Ref. 5). None of the side effects were serious. Marketing data provided by the manufacturer indicate the following consumer complaints based on millions of pulvules distributed annually. Of 31 therapeutic-type consumer complaints received by the manufacturer over almost 5 years, 21 related to lack of benefit. The remainder related to diverse conditions, which probably were associated with ENTORAL only temporally.

c. *Labeling.* Although cautiously worded, the statement on use of the vaccine does imply effectiveness, but the implication is not supported by the evidence. Capsules need to be opened to provide half-doses for infants and young children. If a legitimate indication exists for treating this age group, then half-dose capsules should be available.

3. *Conclusion*—a. *Critique.* Although it may be granted that killed oral vaccine can stimulate some humoral antibody production in man, there is no evidence that such antibody has any protective effect on upper respiratory bacterial infections. In fact, no direct proof exists that the organisms used in the vaccine are even significant as pathogens complicating the common cold. If a true bacterial infection were to develop, antibiotic treatment would be necessary and reliance on such vaccines might delay treatment to the detriment of the patient. In addition, the vaccine has long since been put to the test of controlled clinical studies and found wanting.

b. *Recommendations.* It is recommended that this product be placed in Category IIIB and that the appropriate organism license(s) be revoked for the following reason: There is no substantial or presumptive evidence of effectiveness.

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RESPIRATORY UBA (UBA–32); MIXED VACCINE NO. 4 WITH H. INFLUENZAE (V–306); AND COMBINED VACCINE NO. 4 WITH CATARRHALIS (V–151) MANUFACTURED BY ELI LILLY AND CO.

1. *Description*—a. *Composition*—(1) *Respiratory UBA (UBA–32):*

Organisms	Number of strains	Percent	Milligrams nitrogen per milliliter
Streptococci	7	30	0.015
Pneumococci	4	30	.015
Hemophilus influenzae	2	20	.01
Staphylococci	3	15	.0075
Neisseria catarrhalis	2	5	.0025

(2) *Mixed Vaccine No. 4 with H. Influenzae (V–306):*

Organisms	Number of strains	Millions of organisms per milliliter
H. influenzae	2	500
N. catarrhalis	4	100
Streptococci	6	500
K. pneumoniae	1	150
Staphylococci	11	100
Pneumococci	4	1,500

(3) *Combined Vaccine No. 4 with Catarrhalis (V–151):*

Organisms	Number of strains	Millions of organisms per milliliter
N. catarrhalis	4	200
K. pneumoniae	1	200
Pneumococci	4	100
Streptococci	6	100
Staphylococci	11	600

b. *Preparation*—(1) *Respiratory UBA (UBA–32).* This product is prepared by growing individual strains in mass cultures, washing in Locke's solutions to remove metabolites and fragmenting the bacterial cells in a ball mill as described by Krueger (Refs. 1 and 2 below), and, Powell and Jamieson (Ref. 3). The initial washing is said to remove extra-cellular metabolites and culture components, and the grinding in a ball mill with subsequent filtration is claimed to produce less denaturation of protein than other methods of killing. The ground material is suspended in Locke-Ringer's solution and filtered through acetic-collodion ultrafilters. Standardization of the sterile filtrate is made on the basis of native protein content. Thimerosal, 1:20,000, is added as a preservative.

Strain derivation includes organisms collected from a variety of sources from 1927 to 1948. None of the streptococcal strains are identified as being Group A; three are Group C; one is Group B; and three are nongroupable. Among the pneumococci, Types 1, 2, 5 and 7 are

represented. The two strains of *H. influenzae* are both of type b. The three strains of staphylococci were isolated in 1915, 1929 and 1934; two are *S. aureus* and the third, *S. epidermidis*. The strains of *N. catarrhalis* were obtained in 1934, one from the New York State Health Department Laboratories and the other from Johns Hopkins University. The product is supplied in 20 milliliters rubber-stoppered vials.

(2) *Mixed Vaccine No. 4 with H. Influenzae (V–306)*. This product consists of heat-killed bacteria suspended in isotonic saline. The preservative is 1:10,000 thimerosal. It has four strains of *N. catarrhalis*, two are the same as those in UBA–32 and two are different. One is described as having been obtained from "the sputum of asthma patients" and the other from someone with rhinitis. The six strains of streptococci used in this vaccine are the same as in UBA–32, but the ten strains of *S. aureus* are different in that they were isolated more recently and their phage typing patterns are stated. They represent a variety of types although three are of the 80/81 pattern. An eleventh strain of staphylococcus is the same *S. epidermidis* that is in UBA–32. The four strains of pneumocci are also Types 1, 2, 5 and 7. The one strain of *Klebsiella pneumoniae* was isolated in 1914 by the New York City Board of Health. Standardization of the vaccine is in terms of the numbers of bacteria rather than antigen nitrogen. The product is supplied in 20 milliliters rubber-stoppered vials.

(3) *Combined Vaccine No. 4 with Catarrhalis (V–151)*. This product is a suspension of heat-killed bacteria in isotonic saline with the preservative thimerosal 1:10,000. The method of preparation is the same as in the case of product V–306 as are the strains of *N. catarrhalis*. The four types of pneumococci are, again, Types 1, 2, 5 and 7. Of the six strains of streptococci, one is alpha, two are beta, and three are gamma streptococci according to the hemolysis patterns. Both strains of beta-streptococci are Group C. There are no Group A streptococci in this vaccine. The eleven strains of staphylococci are the same as in V–306. The product is supplied in 20 milliliters rubber-stoppered vials.

2. *Labeling*—a. *Respiratory UBA (UBA–32)*. According to the package insert, the preparation is "intended for cutaneous, intradermal, and topical administration as a means of developing immunity to the organisms represented by the formula." No specific claims of effectiveness are made, but the possibility of improvement in certain patients, namely those with frequently recurring infections and those suspected of having bacterial allergy, is suggested. The types of respiratory infection are not specified, but mention is made of the prophylaxis of respiratory bacterial infections and treatment of chronic suppurative sinusitis.

One dosage schedule is that used by Diehl et al. (Ref. 19) which suggests "prophylaxis of respiratory bacterial infections." Subcutaneous injections of 0.5 milliliter are given twice weekly for 3 weeks, and then 0.5 milliliter every 2 weeks through the fall, winter and spring. It is not stated whether this is to be repeated annually or whether a single course is sufficient. If one is treating "chronic suppurative sinusitis," then "best results have followed subcutaneous, intradermal and topical administration at each visit." When given intranasally, it is suggested that "1.0 to 1.5 milliliters of the product be diluted with an equal quantity of 1- percent epinephrine or other vasoconstrictor in physiological saline." Nothing is mentioned about precautions in the use of such a dose of epinephrine in the presence of certain conditions such as hypertension. Precautions mention the possibility of hypersensitivity reactions, but no mention is made of possible induction of asthmatic attacks. Induction of bronchospasm in asthmatics has been reported to be produced by the inhalation of an aerosol of *N. catarrhalis*. It was felt that this did not represent infection, but rather hypersensitivity (Ref. 20). The user is advised that "precaution of denaturation of the antigen should be observed," but no further explanation or clarification of this statement is given. Dosage for children is not mentioned.

b. *Mixed Vaccine No. 4 with H. Influenzae (V–306)*. The indications for this product are expressed somewhat differently as "a means of developing immunity to organisms represented in the formula." This statement is qualified by citing differences of opinion regarding the effectiveness of bacterial vaccines in decreasing the incidence or severity of respiratory infections. It is stated that improvement often follows administration in patients with frequently recurring infections and those suspected of having bacterial allergy. Implied is the assumption that the organisms from which the product is prepared are responsible for respiratory infections when in fact *N. catarrhalis* and *S. epidermidis* are considered nonpathogenic inhabitants of the respiratory tract.

Injections of the product are recommended for the fall and to be maintained throughout the cold weather. The suggested starting dose is 0.1 to 0.25 milliliter which is increased at 7-day intervals for 4 weeks, and then repeating the maximum dose (usually 1 milliliter) at intervals of 3 to 4 weeks to "maintain immunity." Dosage in children is not given.

Adverse reactions are stated as being due to bacterial allergy, illustrated with an example of the induction of asthma in an asthmatic patient with bacterial allergy. Induction of bronchospasm in asthmatics has been reported to be produced by the inhalation of an aerosol of *N. catarrhalis*. It was felt this did not represent infection but rather hypersensitivity (Ref. 20).

c. *Combined Vaccine No. 4 with Catarrhalis (V–151)*. Indications and precautions are the same as for product V–306. The same assumptions are made that the organisms in the formula are responsible for respiratory infections, when in fact several are normal inhabitants of the respiratory tract.

The suggested dosage schedule recommends the subcutaneous administration of an initial dose of 0.1 milliliter, followed at 5-day intervals by 0.25 milliliter, 0.5 milliliter and 1.0 milliliter. A monthly maintenance dose of 1.0 milliliter is suggested throughout the winter months. Instructions are given for decreasing the dose if a reaction occurs. For small children, the dosage may be reduced, but this is not a firm recommendation and thus not very useful. The induction of bronchospasm as evidence of hypersensitivity to *N. catarrhalis*, mentioned above, also is pertinent.

3. *Analysis*—a. *Safety*—(1) *Respiratory UBA (UBA–32)*. The company submitted animal safety test results obtained over a 7-year period. These conform to regulations on general safety.

Human safety studies are not presented, but the absence of reports of serious reactions over the many years that the vaccine has been in use is cited as evidence of safety. Dose-related reactions are to be expected in the use of such vaccines and the manufacturer recommends that any dose which results in a marked local or systemic reaction should be reduced on subsequent injection, and then gradually increased in repeated injections. Eighteen therapeutic complaints, 13 local reactions and five systemic reactions, are recorded. None is listed as a severe or prolonged illness, but clinical details are not given. Systematic analysis and long-term followup are lacking.

(2) *Mixed Vaccine No. 4 with H. Influenzae (V–306)*. No studies are presented except those required by the FDA for general safety. Human safety data are lacking. The statement is made that no complaints have been received from users of this vaccine.

(3) *Combined Vaccine No. 4 with Catarrhalis (V–151)*. Animal safety data are limited to that required by FDA regulations for general safety. No human safety data are presented except for a report of one adverse reaction during a 6-year period. This is described as "sunburn-like" but with no further details.

b. *Effectiveness*—(1) *Respiratory UBA (UBA–32)*. The background of effectiveness is based on 12 medical references (Refs. 1 through 12 below) three of which (Refs. 4, 10, and 11) deal with *H. pertussis*, an organism which is not used in this product. It is only in these *H. pertussis* reports that one finds any information on the effects of UBA on antibody production and resistance to challenge with virulent bacteria. Other references describe the Krueger method of preparation and use of the product in sinusitis and asthma. Clinical results are reported as variable, but generally favorable and with few adverse reactions. Womack (Ref. 5) reported on the treatment of 53 cases of acute respiratory in-

fections with overnight "cure" in 40 percent of the cases, "good" improvement within 48 to 72 hours in 31 percent of the cases, "fair" improvement over a 5-year period in 25 percent of the cases, and no effect in 4 percent of the cases. No bacteriologic studies were performed and no other treatment is mentioned. Patients who relapsed within 10 days were subsequently treated with injections of the product 3 times weekly for at least 2 weeks. Chronic cases were treated for 6 to 8 months. Ten cases of furuncles of the external ear were treated, all cured. Only one local reaction was observed.

Hosmer (Ref. 9) reported treating 50 patients with chronic sinusitis, of whom 62 percent had good results. All were selected as treatment failures with other types of therapy. Cultures obtained from 50 patients showed hemolytic *S. aureus* to be the most frequent organism present.

Six other references were provided by the manufacturer, none of which has direct application for supporting the effectiveness of the product under consideration (Refs. 13 through 18).

(2) *Mixed Vaccine No. 4 with H. Influenzae (V–306) and Combined Vaccine No. 4 with Catarrhalis (V–151)*. No data are provided to demonstrate antibody responses in either animals or humans with these two products. Evidence in support of human effectiveness is based on availability and clinical usage of these products for many years.

4. *Conclusions*—a. *Critique*—(1) *General*. These products were developed at a time when neither the etiologies of acute respiratory diseases were clearly understood nor the specific antigenic components of the bacteria contained in the products clearly defined. It is now accepted that 90 percent or more of acute respiratory infections are not caused by bacteria but by 300 or more viruses and some mycoplasma. Immunity in the case of bacteria which can be causative is type-specific in the case of *H. influenzae*, pneumococci and streptococci. *N. catarrhalis* is not known to play any role in respiratory infection and immunologic defenses against staphylococci remain to be defined. At best, the latter is only rarely a primary factor in respiratory disease.

The uses for which these products are recommended tend to confuse the issue further. They are claimed to increase immunity to the bacteria from which they are made through repeated, almost constant usage. On the other hand, the same products are recommended for treatment of patients with "bacterial allergy" and asthma through the mechanism of "desensitization." No evidence is provided which would support the contention that the bacterial components of these products are related to the clinical problems presented by such patients. The data provided are largely anecdotal which makes it impossible to assess the benefits claimed from the products' use. With respect to the two types of products described: one of whole bacterial bodies and the other of "denatured bacterial antigen," there are no data which demonstrate whether the two are interchangeable, or that one is superior to the other. It is possible that the method of preparation may result in lower yields of effective antigens or of selective removal of pertinent cell wall antigens. At the very least, it would be desirable to have valid data from experimental animals and humans indicating that they stimulate the formation of measurable antibodies when administered according to directions. It also would need to be demonstrated that value is to be gained from employing vaccines which contain strains of streptococci which only occasionally produce human infections, and other organisms such as *N. catarrhalis* which do not cause respiratory infection. The rationale for including in these products two different *H. influenzae*, type b strains whose antigen is known to be a specific polysaccharide, or multiple strains of non-Group A streptococci and a strain of Klebsiella require supportive evidence. If these are truly immunizing, then the question can be asked why benefits should only be anticipated during their administration, without apparently inducing residual benefits?

(2) *Respiratory UBA (UBA–32)*. In support of Respiratory UBA (UBA–32), brief reports are presented on the immunization of rabbits with pertussis vaccine prepared by the Krueger method, one showing antibody production and the other resistance to challenge with virulent bacteria (Ref. 4). Antibody responses to the bacterial antigens in UBA–32 apparently have not been studied. None of the submitted clinical trials show appropriate controls (Refs. 5 through 9, and 12).

While several bacterial isolations are reported before instituting "immunization," none show any data concerning the type or frequency of bacterial isolation during or after the "immunization" procedure. Desensitization to bacteria has been suggested by several authors as the mode of action. No data, however, are presented on whether the injection of these products has any influence on immediate or delayed hypersensitivity responses, nor is any data presented which would help support the contention that the recipients were hypersensitive to any bacteria in the first place. In treating those with chronic sinusitis, three of the authors specified that the subjects who were included had proven refractory to other forms of treatment, thus making them their own controls. This type of analysis is limited by the subjective nature of the criteria for improvement and by the lack of any precise definition of the natural history of the disease. One partially controlled study which used the Krueger preparation was that of Diehl et al. (Ref. 19) who reported a 25 percent greater reduction in the average number of colds in inoculated subjects as compared to controls. These authors considered the difference statistically significant, but concluded that it was not sufficiently great to warrant use of this product. Although referred to in the package insert, this article was not included in the manufacturer's presentation.

(3) *Mixed Vaccine No. 4 with H. Influenzae (V–306) and Combined Vaccine No. 4 with Catarrhalis (V–151)*. Support for effectiveness of the two other products, Mixed Vaccine No. 4 with *H. Influenzae* (V–306) and Combined Vaccine No. 4 with Catarrhalis (V–151), is indeed meager. Little information is submitted upon which to base any claims for inducing either immunity or desensitization to the organisms from which they are prepared. The statement included in the package insert, which claims that the products are useful in persons with bacterial allergy, is not supported by any data which show that the patients treated had such allergy in the first place, or that the vaccine alters such hypersensitivity states in any way. As to safety considerations in humans, the only support cited is the lack of reported serious adverse reactions during the marketing experiences of the products.

b. *Recommendations*. The data submitted do not adequately prove the effectiveness and safety of any of these three products. Randomized, controlled double-blind studies in accord with the Panel's position on these subjects as part of their general findings are desirable to support effectiveness. Similarly, the period of marketing is not in itself adequate support of safety of these products, as pointed out in the Panel's position as part of their general findings.

Since any product administered parenterally involves risk, and the benefits here have not been clearly documented, benefit-to-risk ratio for all three products is considered to be low.

Since the data which suggest safety and effectiveness are largely based on experience with UBA-32 and there are no data concerning the use of V-306 and V-151, it is recommended that any further studies to substantiate the claims of safety and effectiveness be directed towards the first product.

(1) *Respiratory UBA (UBA–32)*. It is recommended that this product be placed in Category IIIA and that the appropriate license be continued on an interim basis in accordance with the appropriate Federal regulations and recommendations of this report. The reason for this recommendation are that:

(i) There is no substantial evidence of safety and effectiveness.

(ii) There is evidence presumptive of safety based on published reports.

This recommendation to permit continued use of UBA–32 during a test period is made on the condition that no strains of Group A streptococci will be contained in the product in accord with the Panel's statement on this subject as part of their general findings.

Changes in labeling for UBA–32 are required to state clearly the specific indications for use expressed in standard medical terminology. Claims that this product induces either protective immunity or desensitization should be modified

to indicate to the user that these are possible effects that have not been proven. Since there is no conclusive evidence that treatment with this product induces a beneficial effect, claims or implications milliliter, followed by increments to 1 such time as they might be substantiated by further study. Also see labeling statement.)

(2) ***Mixed Vaccine No. 4 with H. Influenzae (V–306) and Combined Vaccine No. 4 with Catarrhalis (V–151)***. It is recommended that these two products be placed in Category IIIB and that the appropriate license(s) be revoked for the following reasons:

(i) There is no substantial evidence of safety or effectiveness.

(ii) There is no evidence presumptive of safety.

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STAPHYLOCOCCUS VACCINE (V–563) MANUFACTURED BY ELI LILLY AND CO.

1. *Description*. The product is a heat-killed suspension of staphylococci (10 strains of *Stapylococcus aureus* and 2 strain of *Staphylococcus epidermidis*) in saline containing thimerosal 1:10,000 as preservative. The vaccine contains 2,000 million *Staphylococcus aureus* and 2,000 million *Staphylococcus epidermidis* organisms per milliliter and is supplied in 5-milliliter-stoppered vials. The sources of all of the bacterial strains are provided in the submission. This includes the phage type and hemolysis patterns of the *Staphylococcus aureus* strains.

2. *Labeling*. The product is suggested for use in chronic or recurrent staphylococcal infections. Other concurrent treatment (antibiotics) also is recommended. Lack of unanimity as to effectiveness of this treatment is noted in the package insert (Refs. 1 through 5 below).

Dosage is variable and depends on patient response. An initial dose of 0.1 milliliter at 3- to 7-day intervals, is the suggested schedule. Adverse reactions such as local redness and constitutional signs such as headache, backache, and lassitude may occur a few to 24 hours after injection. A reaction requires reduction in the next dose. An allergic response to a bacterial vaccine is a contraindication for its use.

3. *Analysis*—a. *Safety*. The animal safety tests are performed as described in 21 CFR 610.11. Conclusions as to human safety are based on the absence of reported adverse reactions during a long period of use.

b. *Effectiveness*. Animal and human effectiveness data were not provided

4. *Conclusions*—a. *Critique*. There is no available information for making a judgment concerning the safety and effectiveness of this product. There is potential harm in repeated injections of foreign material without adequate justification (Refs. 6 and 7). The statement in the package insert, "the immunity which can be produced by staphylococcal vaccines is often useful," is not supported by facts.

b. *Recommendations*. It is recommended that this product be placed in Category IIIB and that the appropriate license(s) be revoked for the following reasons:

(1) There is no substantial evidence of safety or effectiveness.

(2) There is no evidence presumptive of safety.

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V–677 STREPTOCOCCUS VACCINE (INTRAVENOUS) MANUFACTURED BY ELI LILLY AND CO.

The description by Swift (Ref. 1 below) in 1928 of the development of skin allergy in rabbits injected with streptococci and its loss following intravenous administration of the same organisms leads to their consideration as being hypothetically related to the pathogenesis of rheumatic diseases. Clawson reported (Ref. 2) that intradermal injections of alpha hemolytic streptococci produced similar skin reactions in rheumatic patients, furthering interest in such organisms as causal agents of acute rheumatic fever. Following these observations came other reports of the similarities between skin reactions in rabbits and rheumatic patients and suggested potential benefits from intravenous injections of alpha hemolytic streptococci into rheumatic patients (Ref. 3). Later, this was extended to include patients with "chronic" arthritis. The reports of the isolation of alpha hemolytic streptococci from subcutaneous nodules removed from patients with acute rheumatic fever (Ref. 5) and chronic arthritis (Ref. 4), and from the bloods of patients with chronic arthritis (Refs. 6 and 7), suggested the concepts of cause and treatment in the minds of some clinicians.

The papers submitted by the manufacturer detail this history and outline the studies of Wetherby and Clawson (Ref. 3) and Wetherby (Ref. 8) which

attempted to document the value of intravenous streptococcal treatment of chronic arthritis. These authors noted a lack of uniformity in the diagnoses of their treated cases, varying from rheumatic fever to osteoarthritis. They also believed (despite the variety of diagnoses) that the presence of streptococci in the blood streams of patients with chronic arthritis implied an etiologic relationship between the two.

The bulk of the patients described by Wetherby (Ref. 11) were treated with vaccines made from alpha hemolytic streptococci (not the gamma organisms used in the V–677 vaccine under discussion) and at one time considered to be causally related to rheumatoid arthritis. He treated 4,000 patients with "rheumatoid complaints" and with diagnoses varying from hypertrophic osteoarthritis to rheumatic fever at the University of Minnesota Hospital during a 9-year period. About 90 percent of the patients were said to have had symptoms for more than a year. Among 1,192 consecutive patients (from the larger group) with "chronic arthritis" treated with intravenous vaccine, 75 percent were "definitely improved," 10 percent "questionably improved," and 15 percent "not improved" during 6 to 24 months of observation. Recognizing that these were uncontrolled observations, the author undertook another study which is described in the same paper. In this study, 80 rheumatoid arthritic patients were treated alternately (without selection) with either vaccine or sterile saline supplied from bottles identified as A or B. Among the vaccine-treated, 82 percent "improved" as opposed to 40 percent in the saline-treated group.

The investigator's objective in this "mini" trial was laudable and its design adequate for its time, but it has deficiencies which seriously impair its current usefulness. For example, no attempt was made to randomize recipients but rather, they were alternated. The latter system fails to avoid selective biases and is not acceptable. Secondly, only two label identifications (A and B) were used for the vials so that reactions could be quickly associated with one or the other and the "code" easily broken. No information is supplied to indicate that patients in the two groups were paired for variables such as diagnosis, age, sex, sedimentation rate, duration of illness, number of joints involved, etc. Responses were estimated subjectively by different observers. It is stated that each patient received "eight weekly injections of increasing dosage" and "if improved," continued at 4-week intervals. Presumably, then, those in the "no improvement" category were dropped after 8 weeks, but this is not stated, nor are there any data concerning their outcomes and whether they might have improved subsequently. Thus there appear to have been unequal (and unaccounted) followup periods for individual participants. All estimates of change were arrived at by three staff members from reviews of patient records. All are said to have concurred as to the clinical results as recorded. It is not stated whether any of the three had also recorded primary responses as patient-care physicians.

Reactions to the intravenous vaccine are described as minor (chills, fever, nausea) with no deaths being recorded after 100,000 injections in 4,000 patients. One death is described in a chronic arthritic patient; it was demonstrated postmortem that the patient had amyloid disease. This relationship is not analyzed further. Alarming reactions are ascribed to vaccines made from beta hemolytic streptococci but are not further detailed. The author mentions the difficulty of evaluating such vaccine therapy because of a variety of therapeutic variables such as rest, avoidance of cold and trauma. The vaccine used in the Wetherby study appears to have been made from alpha rather than gamma streptococci and was not produced by the manufacturer of this product under review.

Although the data (experimental and clinical) presented by Swift (Ref. 1), Clawson and Wetherby (Ref. 3) resulted in reasonable conclusions based upon the then available evidence, alpha hemolytic streptococci have not been considered to be causally related either to rheumatic fever or to rheumatoid arthritis for many years. The demonstration that minimal dental manipulation often results in alpha or gamma streptococcal bacteremia may explain the frequency of isolations of such organisms in blood cultures (Ref. 9). The lack of toxicity of nonpathogenic streptococci which may frequently invade the blood stream in the course of many normal activities is therefore not entirely surprising.

1. *Description.* The vaccine consists of heat-killed gamma hemolytic streptococci of a strain used by Clawson and Wetherby for the treatment of chronic arthritis. One milliliter contains 400 million organisms suspended in isotonic sodium chloride solution with merthiolate (thimerosal, Lilly) 1:10,000 added as a preservative.

The manufacturer's marketing data records 18 reactions, such as chills, fever, aching and nausea, between May 1972 and December 1973, following injections with four lots of vaccine. An increased incidence of febrile reactions in 1951–1952 is discussed in a series of letters between Dr. M. Wetherby and the Lilly Biological Research Division. This increase was ascribed to a change in the medium used to cultivate the bacteria for the vaccine.

2. *Labeling.* Indications for V–677 vaccine's use are based upon the concept that bacterial allergy plays a role in the etiology of rheumatoid arthritis. Desensitization by serial injections of this streptococcal vaccine is recommended as an adjuvant to other forms of treatment of this disease. The manufacturer's insert states that there is a lack of unanimity among medical observers as to the value of such vaccine treatment and warns that it not be administered to those who are pregnant or have glomerulonephritis.

3. *Analysis*—a. *Safety.* The available data suggest that though reactions do occur with nonhemolytic streptococcal vaccines, organ pathology or directly related deaths have not been recorded. This presumed safety may be more apparent than real and only a reflection of the intensity with which sophisticated investigative methods have been employed. For example, in clinical situations, such as subacute bacterial endocarditis, where chronic infections with nonpathogenic (alpha and gamma hemolytic) streptococci are seen, conglutinin (positive latex agglutination) titers and immune glomerulonephritis may be found (Ref. 14). These observations pose questions of safety with regard to the chronic injection of such material into humans.

b. *Effectiveness.* The data presented by Wetherby and Clawson (Refs. 3 and 10) and Wetherby (Refs. 8 and 11) indicating improvement in 75 to 82.5 percent of patients treated with intravenous streptococcal vaccines as compared to 40 percent improvement in a "control" group treated with saline solution already has been discussed. At first glance this would appear to be significant were it not for the defects previously noted in the study. The variability of the clinical course of rheumatoid arthritis was referred to by the different authors. To this should be added that rheumatoid arthritic patients most likely to have complete remissions are those who have had the disease for less than 3 years (Ref. 12). The majority of Wetherby's "chronic arthritis group" fell into this range. As such, a large proportion might have been expected to remit or improve spontaneously, independent of treatment. The duration of symptoms among the 80 rheumatoid patients who were studied in the controlled study was not provided, adding another uncontrollable variable to a "controlled" study. The inconclusive nature of this, the only "controlled" study with streptococcal vaccine (different from the V–677 product) does not provide the data required for a positive judgment of the safety or effectiveness of V–677. The etiology of rheumatoid arthritis remains unidentified but the overwhelmingly negative results of many bacteriological studies indicate that it is unlikely that rheumatoid arthritis is the result of any easily culturable or characterized bacterium (Ref. 13).

4. *Conclusions.* It is recommended that this product be placed in Category IIIB and that the appropriate license(s) be revoked for the following reasons:

a. There is no substantial evidence of safety or effectiveness.

b. There is no evidence presumptive of safety.

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STAPHYLOCOCCUS–STREPTOCOCCUS UBA (UBA–48), UNDENATURED BACTERIAL ANTIGEN) MANUFACTURED BY ELI LILLY AND CO.

1. *Description*—a. *Composition.* Staphylococcus-Streptococcus UBA, undenatured bacterial antigen) contains undenatured antigens of staphylococci and streptococci standardized to 0.5 milligram of nitrogen per milliliter. Two strains of *Staphylococcus aureus*, one strain of *Staphylococcus epidermidis*, four strains of ungroupable streptococci (one of which is identified as the Clawson-Wetherby Strain), and three groupable strains of streptococci (two Group C and Group B) are listed as the constituents of the vaccine.

b. *Preparation.* The antigens are prepared by grinding the organisms in a ball mill, as described by Krueger (Ref. 1 below) and by Powell and Jamieson (Ref. 2). The ground material is then suspended in Locke-Ringer's solutions and passed through sterile filters. Thimerosal, 1:20,000, is used as a preservative.

Since heat and chemicals are not used in the manufacturing process, it is thought by the manufacturer that denaturation of the bacterial protein does not occur and, therefore, that immunization is more likely to be specific.

2. *Labeling.* The indications for use of this preparation are described as being intended for treatment of mixed staphylococcus and streptococcus infections, chronic arthritis, and as an adjunct to therapy in cases of acne complicated by pyogenic infection.

Adverse reactions are described as locations consisting of redness and swelling at the injection site due to hypersensitivity to the vaccine, such a reaction being an indication for a reduction in dosage. Inflammatory focal reactions are cited as occurring at the site of the disease being treated. It is also noted that inflammation in the joints in cases of arthritis may be increased, or pustular lesions may be temporarily more severe. Such reactions as noted are to be avoided through reduction of the individual doses employed.

Epinephrine 1:1,000 and other emergency drugs and equipment are recommended to combat severe systemic reactions if they develop.

It is recommended that dosage be individualized. If the initial dose of 0.1 milliliter subcutaneously produces a local reaction, it should be reduced to 0.01 milliliter or less. If no reaction occurs, the prescribed dose is to be increased by 0.1 milliliter with each injection. Injections are to be given two or three times a week until improvement is maintained without focal reaction.

3. *Analysis*—a. *Safety.* Animal safety tests are performed as described in 21 CFR 610.11.

Human safety data are presented in the form of marketing data and in the statement that during a period of 7 years, four complaints were received. The nature of the complaints is not cited.

No specific documentation is cited by the manufacturer for safety of the product. Staphylococcal antigens have been described to induce altered states of mammalian tissue reactivity (Refs. 3 through 5). A recent report of accelerated skin graft rejection occurring in a human with *Staphylococcus aureus* and Group A streptococcus infection (Ref. 5) is noted.

b. *Effectiveness.* No documentation of effectiveness is provided in published reports.

Effectiveness is questioned in the absence of evidence of demonstrated antigenicity or of clinical evidence of response in a defined disease state.

One paper that is directly related to this agent is found in the manufacturer's submission for respiratory UBA. The paper by Schallig (Ref. 6) describes the treatment of "chronic arthritis" with UBA Staphylococcus-Streptococcus, 0.5 cubic centimeter intramuscularly biweekly. One hundred patients are recorded as receiving the vaccine with 65 percent being completely relieved of their symptoms within 10 weeks of instituting therapy. An additional 25 percent are described as responding within 10 to 25 weeks of starting therapy. Systemic reactions are recorded as not occurring. The lack of diagnosis, controls and objective criteria for measuring response renders this report virtually useless for evaluating the product.

4. *Conclusions*—a. *Critique.* The paucity of data makes meaningful evaluation of Staphylococcus-Streptococcus UBA difficult. Labeling is therefore at best inaccurate.

Safety would appear to present no major problems on the basis of the manufacturer's marketing data. There is, however, evidence that streptococcal and staphylococcal antigens are capable of inducing altered tissue reactivity in mammals.

b. *Recommendations.* It is recommended that this product be placed in Category IIIB and that the appropriate license(s) be revoked for the following reasons:

(1) There is no substantial evidence of safety or effectiveness.

(2) There is no evidence presumptive of safety.

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BACTERIAL VACCINE MADE FROM TYPHOID H. ANTIGEN (B–763 TYPHOID H. ANTIGEN), MANUFACTURED BY ELI LILLY AND CO.

1. *Description.* The product is a suspension of organisms from cultures of motile *Salmonella typhosa* in isotonic sodium chloride. The organisms are killed by 0.5 percent phenol, which probably fixes the flagellar (H) antigen on the surface of the cell without inactivating this antigen (Ref. 1 below). The final product contains 25 million killed organisms per milliliter.

2. *Labeling.* The package insert states that the antigen is intended for the production of a nonspecific febrile response following intravenous administration, which may be useful in certain infections and inflammations of the eye, particularly of the uveal tract (Refs. 2 and 3). Reference also is made to its use to prevent postoperative eye inflammation (Ref. 4).

3. *Analysis*—a. *Effectiveness.* The package insert describes the expected febrile response following intravenous administration of the vaccine. In this restricted sense, the vaccine is potent. It is highly probable that potency is related to the somatic antigen and/or endotoxin

rather than to the H antigen, which lacks a significant biological effect except to stimulate antibody production. The vaccine came into use in the 1930's as one of various types of substances used in nonspecific "protein therapy" such as boiled milk, autogenous blood, vaccinia, placental implantation, and diphtheria antitoxin (Refs. 3 and 5). Brown claimed that the vaccine was more effective than these other agents and "less shocking" than conventional typhoid vaccine. He also proposed that the therapeutic effect was due to stimulation of H antibodies rather than to the production of fever—a most speculative concept, since the etiology of most cases of uveitis was completely unknown and remains so today and there is no evidence that typhoid has any role in uveitis.

The company submitted three published papers in support of effectiveness. One is a report on the effect of vaccine on staphylococcus-induced corneal ulcers in rabbits and seven human cases (Ref. 2). Another relates to its prophylactic use before intraocular operations (Ref. 4). One deals with uveitis and consists of five case reports, plus a summary discussion of the author's general treatment of 40 patients that provides meager information regarding the effectiveness of the vaccine itself (Ref. 3). There have been no controlled or partially controlled studies, and no other data were submitted to the Panel from any source.

The modern concept regarding the possible benefit of fever therapy is that it stimulates adrenocorticotropin and glucocorticoid production. This was established in 1956 by Donn, who observed a rise in plasma corticoid levels after injection of conventional Typhoid-AB vaccine that was comparable to that produced by ACTH (Ref. 6). No studies have been done to show that typhoid H vaccine has this effect, but there is little doubt that it does. Despite some claims to the contrary (Ref. 7), there is no reason to expect this would have any advantage over direct corticosteroid treatment.

Modern authorities refer to typhoid vaccine as available treatment for uveitis, but without much enthusiasm or documentation. Two recommended that it should be abandoned in favor of safer modes of therapy (Refs. 5 and 7). Typhoid H antigen was cited as one form of treatment for anterior uveitis in the 1968 edition of "May's Diseases of the Eye" (Ref. 8). Several forms of nonspecific therapy were discussed by Coles in a 1972 text, including "Triple Typhoid H antigen," with the qualifying statement that such treatment "has limited usefulness, and with the advent of steroids there is little indication for its use" (Ref. 9). In one of the most authoritative and newest texts, such treatment is relegated to three lines as "mainly of historical interest" (Ref. 10).

b. *Safety.* Available animal safety data is limited to the general safety test required by FDA regulations (21 CFR 610.-11), and the published report on corneal ulcers in rabbits (Ref. 2). Support for human safety consists of five published papers, which were submitted by the company (Refs. 2 through 4 and two papers on the use of the product for peripheral vascular disease). Other than the anticipated toxic reactions ("shock") for which it became prudent to hospitalize patients before giving the vaccine there was practically no mention of adverse reactions, except in the peripheral vascular disease patients, in whom 3 of 150 developed femoral artery thrombosis, acute hemorrhagic enteritis, and recurrence of quiescent iritis reactions (Ref. 11). Reference is made to arterial thrombosis in another paper as being noted by several observers, but it is not clear whether these events were related to typhoid H or to Typhoid-AB vaccines (Ref. 12).

No complaints of adverse effects were received by the company over a period of almost 6 years, during which time some thousands of vials of vaccine were sold. So little has been published regarding the use of typhoid H vaccine that it is necessary to look at the record of typhoid vaccine in general to gain a more adequate impression of its safety, and the record is hardly reassuring. Several fatal reactions have occurred. In 1944, Urbach et al. (Ref. 13) reported a death with features of the generalized Sanarelli-Shwartzman phenomenon following the intravenous injection of "triple typhoid" to a patient with arthritis and made reference to other reports of sudden death. Another fatality with disseminated intravascular coagulation occurred after injection with typhoid vaccine (type not specified) intravenously to a patient with uveitis. This was reported by Aronson, who stated it would be virtually impossible to predict who would have a lethal reaction (Ref. 5). Block-Michel has stated that "vaccinotherapy is relatively dangerous and should be abandoned," but he did not support this statement with specific case records (Ref. 7). Despite the lack of such reports following typhoid H vaccine, the Panel must be concerned about the potential risk in giving this vaccine when used to produce a biological effect so similar to that induced by these other vaccines.

c. *Labeling.* The package insert is misleading in several particulars.

(1) The product contains substantial biologically active material besides the H antigen.

(2) The indications for use have no scientifically documented support other than the expected production of fever. Use for infections of the eye would be inappropriate and could well delay more specific treatment.

(3) The heterogeneity of disorders involving the uveal tract is not mentioned.

(4) The potential for severe adverse reactions is not adequately emphasized.

4. *Conclusions.* Typhoid H antigen has been used for its fever producing qualities but there is insufficient evidence for effectiveness to justify the risk of treatment with it.

It is recommended that the product be placed in Category IIIB, and that the appropriate organism license(s) be revoked for the following reasons:

a. There is no substantial evidence for safety and effectiveness.

b. There is no evidence presumptive of safety, and a lack of safety is suggested by the composition of the product.

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RESPIRATORY BACTERIAL ANTIGEN COMPLEXES (B.A.C.): RESPIRATORY B.A.C., POOLED STOCK B.A.C. NO. 1, POOLED STOCK B.A.C. NO. 2, AND GRAM NEGATIVE B.A.C. MANUFACTURED BY HOFFMANN LABORATORIES, INC.

License to manufacture B.A.C. products was originally granted in 1956. The manufacturer describes these preparations as "polyvalent acellular complexes" which are produced through a—

unique manufacturing process resulting in diffusible bacterial antigens modified to be nontoxic when injected intraperitoneally into mice and guinea pigs at levels in the range of 1,500 times the maximum dose recommended for intradermal or subcutaneous administration into humans.

B.A.C. preparations are therefore claimed to represent sterile, acellular, aqueous solutions of bacterial antigens, free of bacterial cells.

The basis for B.A.C. products dates back to the 1940's when Hoffmann Laboratories first used autogenous cultures of respiratory flora to prepare their special bacterial antigens. From autogenous preparations, the manufacturer progressed to mixtures of bacterial antigen concentrates, which were varied from year to year on the basis of the particular microorganisms reported by public health surveys to have high incidences in patients with respiratory illness. In 1968, the Division of Biologics Standards directed that fixed groups of bacterial cultures be selected, and used thereafter in the preparation of Hoffmann products.

The rationale of B.A.C. effectiveness is based on the following premise as taken from their advertising:

> Protective immunization can best be induced by the use of live bacteria and viruses which produce toxins and enzymes to manifest varied forms of disease. Since the use of live bacteria in man is not feasible, combination of toxins, enzymes, and somatic antigens into a B.A.C. preparation can produce a succession of events which approximates that of actual infections. B.A.C. is capable of stimulating the formation of antibodies, some of which are capable of neutralizing these same toxins and enzymes, thereby accelerating the healing process and eliminating the infection.

It is the manufacturer's contention that strains of organisms subjected to their special manufacturing technique provide important antigens lacking in standard mixed bacterial vaccines prepared by conventional methods.

1. *Description*—a. *Composition*—(1) *Products.* Four respiratory products are currently marketed. Their composition as expressed in terms of percentages of bacterial antigen concentrates are as follows:

Product component	Percent of antigen concentrate
(i) Respiratory B.A.C.:	
Streptococcus pyogenes (Group A, beta hemolytic strep.), autogenous, and types 3, 4, 10 and 12	17.0
Streptococcus viridans (alpha hemolytic strep.)	15.0
Streptococcus faecalis (nonhemolytic strep.)	4.0
Diplococcus pneumoniae, autogenous and types I, II, III, V, VI, VII, XIV, and XIX	22.0
Staphylococcus aureus and *albus*	24.0
Escherichia coli	6.0
Haemophilus influenzae	6.0
Neisseria catarrhalis	6.0
(ii) Gram-negative B.A.C.:	
Pseudomonas aeruginosa	32.0
Escherichia coli	45.0
Aerobacter aerogenes	23.0
(iii) Pooled stock B.A.C. #1:	
Streptococcus pyogenes (Group A, beta hemolytic strep.) types 3, 10, 12 and Granger	16.0
Streptococcus viridans, (alpha-hemolytic strep.) R1551, R1822, and R353	10.0
Diplococcus pneumoniae, types I, II, V, VII, and XIV	35.0
Staphylococcus aureus and albus	20.0
Escherichia coli	5.0
Haemophilus influenzae, types A and B	10.0
Neisseria catarrhalis	5.0
(iv) Pooled stock B.A.C. #2:	
Streptococcus pyogenes (Group A, beta hemolytic strep.), types 14, 18 and 19	40.0
Diplococcus pneumoniae, types III, VI, and XIX	32.0
Klebsiella pneumoniae, type A	8.0
Pseudomonas aeruginosa	6.5
Escherichia coli	7.0
Aerobacter aerogenes	6.5

(2) *Basis for selection of organisms.* In the development of these products, organisms were isolated from individual patients suffering from chronically recurring upper respiratory infections and asthma. Following identification, autogenous B.A.C. preparations were made for the treatment of these same patients, the surplus powder remaining for each organism was retained and stored, and eventually some of these became the constituents of the first lots of Pooled Autogenous B.A.C. Subsequently the number of species and strains of organisms included in B.A.C. products represented those isolated from patients believed to have bacterial allergy as one component of their illness. Selection was further guided by the composition of polyvalent bacterial vaccines of other manufacturers, and the published and personal communications of various investigators.

A so-called "set of eight B.A.C.'s" is constantly referred to in the manufacturer's literature and represents eight groups of bacteria. These are listed as various types of Beta hemolytic streptococci, Group A; pneumococcal types most prevalent in adults; pneumococcal types most prevalent in children; *Streptococcus viridans* types; *Staphylococcus aureus* and *albus; Neisseria catarrhalis; Hemophilus influenzae A* and *B;* and *E. coli.* This "set of eight" was used by Dalven and Romano (Ref. 13) as well as by Spielman (Ref. 8) in treating child and adult patients with upper respiratory and throat infections, infectious asthma, bronchitis and sinusitis.

The first reference to Pooled Stock B.A.C. #1 is that of Gundy (Ref. 14), who used this combination to treat children with recurrent upper respiratory infections and infectious asthma. Its composition was based on selections from the "set of eight" decided by the manufacturer with the advice of Dr. William B. Sherman, one of the early clinical investigators. According to the submission, the composition of Pooled Stock B.A.C. #2 was determined by Dr. Spielman who recommended that those organisms whose antigens were in the "set of eight" and which had not been used in Pooled Stock B.A.C. #1 should be combined together with antigens from *A. aerogenes, P. aeruginosa* and *K. pneumoniae* to make Pooled Stock B.A.C. #2.

Gram-negative B.A.C., representing combination of antigens from *E. coli, A aerogenes, P. aeruginosa* was formulated on the basis of potential usefulness of such a product in patients who had received prolonged treatment with antibiotics and in whom the bacterial flora had changed from gram-positive to gram-negative.

Respiratory B.A.C. was originally prepared with B.A.C. powders made from *D. pneumoniae, S. pyogenes, S. viridans, S. faecalis, N. catarrhalis, H. influenzae, E. coli,* and varying strains of staphylococci from year to year according to the incidence of their isolates from the respiratory tract. In 1968, on the basis of a directive from the Division of Biologics Standards, the composition of this product was made constant in all subsequent marketing.

b. *Preparation.* Identification procedures of the various microorganisms which serve as the basis of B.A.C. preparations (Refs. 1 through 3) appear in line with accepted methods, and are described extensively in the manufacturer's submissions.

Cultures of each species of microorganism are grown to high titer on various standard culture media, checked for purity, centrifuged, and processed into powders by a method which the manufacturer considers confidential. Preservatives are added, and after sterility tests, the extract is injected intraperitoneally into mice as a preliminary safety test, and then packaged for use. The special process is claimed to be effective in selecting the higher molecular-weight materials from the culture media filtrates in which the microorganisms are grown, as demonstrated by an increase in nondialyzable nitrogen-containing fractions. These fractions are said to contain the antigenic materials produced by the bacteria which are experimentally capable of producing specific agglutinins and precipitins.

2. *Labeling.* B.A.C. respiratory products are claimed to be useful in the treatment of "patients known or suspected to be allergic to bacteria and their metabolites." They also are suggested for use in the treatment of recurrent and chronic bacterial upper respiratory infections, bronchitis, sinusitis and throat infections. In allergic disease complicated by infection, the use of B.A.C. preparations said to be in keeping with the commonly employed medical practice of utilizing bacterial products in the treatment of such illnesses. B.A.C. preparations are claimed to be more effective than conventionally prepared extracts of bacterial cells inasmuch as they contain bacterial antigens shown by experimental data to be more effective in achieving both "protection" and "dissensitization." Stock B.A.C. products are considered by the manufacturer to be more effective than autogenous vaccines, "since different flora exists in different sites, and a seasonal variation in bacteria may be present in infectious foci." Simultaneous treatment with B.A.C. products and inhalant allergens is advised for "concurrent allergic and infectious states with the purpose of increasing resistance to existing and possible future infection."

Administration is recommended in doses of 0.02 to 0.05 milliliter intradermally and 0.035 to 0.10 milliliter subcutaneously. The intradermal route is suggested for best results. Increments are recommended if the patient fails to sustain improvement. The suggested inter-

vals are weekly for 4 weeks, twice biweekly and then once monthly throughout the year. Unspecified variations of intervals according to the response of the recipient are advocated. No more than two B.A.C. products at any one visit are suggested, and pooling of B.A.C. products is not considered advisable. No references are given to indicate the basis for these statements.

3. *Analysis*—a. *Activity and stability data.* An early unpublished report by one clinical investigator, E. Perlman, notes that a B.A.C. filtrate contained immunologically active constituents of each organism from which it was prepared, as determined by agar-gel zone precipitation technique. Data concerning the stability of B.A.C. products was recently supplemented by the manufacturer following initiation of this Panel's review. Immunodiffusion studies were carried out utilizing two lots of one product, Respiratory B.A.C., one lot within the expiration date and the other lot outdated. Each of these was reacted against standard pneumonococcal and streptococcal antisera and showed weak immunoprecipitin lines. Other data submitted were immunodiffusion studies of various lots of the same product, Respiratory B.A.C., in and out of the dating period, against antisera prepared by inoculating rabbits with a previously prepared batch of the same product. Also submitted were data purporting to show stability of five other B.A.C. products, Pooled Stock B.A.C. No. 1, Pooled Stock B.A.C. No. 2, Gram Negative B.A.C., as well as two skin products, Staphylococcal B.A.C. and Pooled Skin B.A.C. Outdated lots of each of these products were used. Quantification of antigen by the polygon plate method was carried out in each case against a corresponding antiserum prepared in rabbits. Immunoprecipitin lines were observed with all but the oldest lots which had expired approximately 5 years before. Least reactivity was noted in one product, Pooled Stock B.A.C. No. 2, which was explained on the basis of a weaker antiserum resulting from inoculating a rabbit with less antigen than was given in preparing antisera against the other products.

b. *Animal experimental data*—(1) *Effectiveness.* Data submitted by the manufacturer are designed to show that immunization of experimental animals with B.A.C. products confers a degree of protection when such animals are challenged with injections of live bacterial cultures (Refs. 4 through 6). Mice receiving immunizing doses of B.A.C. prepared from *staphylococcus* albus 42D (this is a designation used in information submitted by the manufacturer) were challenged 7 days later by intraperitoneal injections of *Staphylococcus albus* 42D culture. Organs from animals sacrificed 4 days after challenge showed fewer positive cultures than among untreated controls. Also reported was the protective effect of the same B.A.C. preparation on a phenomenon described as "crippling" resulting in symptoms of limping and paralysis which are said to follow injections of staphylococcal 42D toxin in mice. Fewer mice receiving multiple injections of B.A.C. prepared from staphylococcal 42D developed the "crippling" phenomenon, when compared to untreated controls, or animals receiving only single B.A.C. immunizing injections. A comparison of the effects of this same B.A.C. preparation and a standard bacterial vaccine (type or method of preparation not specified) is reported. Repeating the above experiments utilizing a conventionally prepared bacterial vaccine in what could be considered as immunizing doses, no protection of the test animals was reported. Experiments were not carried out with organisms other than *Staphylococcus albus* 42D, but the implication is drawn that similar advantages exist in all B.A.C. preparations.

(2) *Safety.* The manufacturer states that intraperitoneal injections into mice and guinea pigs are "nontoxic at levels 1,500 times the maximum doses recommended for intradermal or subcutaneous administration in humans." They also cite experiments in which rabbits who received repeated injections of B.A.C. products (types not specified) over long-term periods showed no degenerative changes in organs or tissues. During 1972–1973, the manufacturer treated mice with each of his B.A.C. products over a 1-year period, utilizing a human regimen with doses of 0.10 cubic centimeter subcutaneously. On a dose-per-kilogram basis, this would represent 1,000 times the human dose. Limited alopecia was observed in some groups of mice. Growth was comparable to controls. Autopsy results of various groups of animals were considered not to show any significant differences from controls. Organs and tissues have been fixed and preserved, awaiting further examination by the FDA, if such is thought to be required.

(c) *Human data*—(1) *Laboratory data.* In the historical development of B.A.C. products, the manufacturer claimed that antigenic activity of the materials obtained by the special manufacturing process is greater than that of conventional extracts of bacterial cells. Very little proof of such advantages in humans is found in the submission data. Although it is stated in the submission that B.A.C. products under review are capable of producing specific agglutinins and precipitins, it is not stated whether these effects were noted in man as well as in animals. H. J. Harris states that Brucella antigens prepared by the B.A.C. process produced serologic responses (type or extent not stated) in a high percentage of patients with Brucellosis who were treated with such antigens (Ref. 7). Other biologic reactions reported are quantitative changes in leucocytes (up or down) 15 minutes following administration of B.A.C. products to patients with arthritis.

(2) *Skin test data.* Observations on skin tests are reported by several observers. Spielman (Refs. 8 and 9) observed immediate whealing skin test reactions in 65 percent of patients he treated. He was unable to correlate such reactions with their clinical response to treatment. For testing, he used B.A.C. preparations of *S. aureus* and *albus; N. catarrhalis; H. influenzae,* types a and b; and *E. coli.* Biopsy of a B.A.C. skin test site (presumably positive-reacting site) showed almost no cellular reaction as contrasted to biopsies of similar sites tested with standard bacterial vaccines. The latter showed marked infiltration and large numbers of leucocytes. He also reported that B.A.C. products, in contrast to standard bacterial vaccines, did not produce delayed 24-hour responses.

It is not stated whether both preparations were compared in the same patient. Repeating such skin tests with B.A.C. in patients who were being treated with a Respiratory B.A.C. combination of these organisms, Spielman reported that skin tests remained positive in some, lessened in others, and became totally negative in still others. Where tests remained positive, passive transfer of sensitivity by serum to another recipient was possible. Details of these experiments were not given and have not been published. Spielman also concluded that patients who showed persistently negative skin tests to B.A.C. products before and after treatment required less treatment than those who reacted strongly. He further concluded that skin test negative patients were probably "not hypersensitive to bacteria, but needed only to be better immunized" (Ref. 9).

According to unpublished reports supplied by the manufacturer, E. Perlman carried out skin tests with filtrates of B.A.C. products and noted both immediate and delayed skin reactions. He concluded that such reactions were not helpful in revealing the type of bacterial allergy present or in gauging the patient's response to such treatment. Sheldon, who carried out a small treatment program in patients with bronchial asthma associated with infection, reported that patients showed immediate wheal and flare reactions to the B.A.C. product he used. The types of B.A.C. product used were not indicated in either Perlman's or Sheldon's work, nor were other details of the experiments provided in any of the above reports.

(3) *Clinical effectiveness.* The manufacturer submitted unpublished reports on clinical trials carried out by several observers. A report by Arbesman (1955) covered patients with bronchial asthma and atopic eczema in whom infectious or bacterial elements were considered to play a role. His general impression was that the material (possibly, Respiratory B.A.C.) "did not induce sufficient benefit to warrant continuation of study." Later, he reported in 1956 on the use of "new Pooled B.A.C. Vaccine," and again he failed to observe striking improvement in patients he treated.

Sherman and Cooke, in 1956, summarized a preliminary uncontrolled trial of B.A.C. preparation (possibly, Pooled B.A.C. #1) in patients with asthma, vasomotor rhinitis, and sinusitis believed

due to bacterial infection. The impression was gained by these observers that B.A.C. had definite value in the treatment of such cases, the results being superior to those observed with whole cell bacterial vaccines, and seemed to warrant further study. Four patients in this series experienced constitutional reactions from the first or second dose of B.A.C. and were dropped from the study.

Perlman, in 1956, found no difference between B.A.C. treated patients and controls. He concluded that "while B.A.C. filtrates contained active materials," as determined by his previous experiments, treatment proved to be no more dramatic or satisfactory than with standard bacterial vaccines in patients with "infectious asthma." Comments from Hoffmann Laboratories take issue with his conclusions and point out that recommended dosage schedules were not employed. Sheldon, in 1955, treated 14 patients, (the type of B.A.C. was not specified) with bronchial asthma initiated by or associated with infection. One patient appeared to be benefited, and possible improvement was reported in three others. Stoesser and Nelson in 1956 utilized two dosage schedules in patients with asthma. The first did not produce any improvement while the second did show improvement in some, but the results were not considered dramatic. The details of their dosage schedules are not included in the data supplied.

Published reports on the use of Respiratory B.A.C. products include those of Spielman (Refs. 8 and 9), Shinefield (Ref. 10), Simon and Rinard (Refs. 11 and 12), Dulvin and Romano (Ref. 13) and Gundy (Ref. 14). All are uncontrolled studies which claimed effectiveness in the treatment of children and adults with recurrent respiratory infections, infectious asthma and chronic lung disease. The B.A.C. products utilized in these studies are not always the same as those presently marketed. No substantial basis could be found for the selection of one product over another for treatment. Spielman (Ref. 8), who appears to have been the prime early clinical investigator for these products, states that:

> selection of a particular pooled group strain depends on the patient's clinical response—only clinical response is used as indication of treatment with a particular preparation.

He indicates that when improvement in his patients was established, an "all-inclusive" B.A.C. was used as a maintenance dose throughout the balance of treatment. Other authors, including Simon and Rinard (Refs. 11 and 12), described their procedure for establishing both dosage and the type of B.A.C. to be used. If a patient showed improvement following two successive doses of an undiluted B.A.C. preparation, they continued to use this product undiluted in a subsequent series of injections. If the patient appeared worse following these initial intradermal injections, the same B.A.C. combination was diluted to 1/100, and a series of gradually increasing doses was used in treatment. The exact dosage and the interval between injections depended on the duration of relief afforded the patient. If the B.A.C. product first used failed to benefit the patient, another B.A.C. preparation was tried, and a similar procedure followed. These authors used four Respiratory B.A.C. products close to the composition of those currently marketed, as well as a fifth preparation called "Special Hospital Staphylococcus B.A.C.," which is listed as containing phage types 42B/52/80/81. They reported improvement in 200 of 300 patients with chronic lung disease, infectious asthma, chronic bronchitis and pulmonary emphysema on this program. One patient who failed to improve with other therapy was subsequently treated with a B.A.C. prepared from organisms isolated from his own sputum and showed improvement (Ref. 15). Shinefield's study (Ref. 10) utilized only autogenous B.A.C. products, comparing them to stock bacterial vaccines. He reported superior results with the B.A.C. preparations.

Numerous letters, depositions and reports from physicians and patients supporting the efficacy of Respiratory B.A.C. products are part of the manufacturer's submission. Many reports were in response to the manufacturer's letter, directed to physician prescribers of these products, indicating that a review was taking place. These cover a wide range of respiratory illnesses and frequently do not specify the type of B.A.C. product used. The manufacturer estimates that these reports show an efficacy rate in the range of 80 percent for all patients treated.

(4) *Safety.* A review of submitted data and published literature shows few instances of acute reactions aside from those associated with local pain or swelling at the site of injection, or an occasional febrile reaction. Among the earlier investigators, Sheldon, Sherman and Cooke reported constitutional reactions from the first or second doses of B.A.C. On the other hand, Shinefield (Ref. 10), who used only autogenous B.A.C. preparations, commented on the lack of untoward reactions from doses several times higher than those recommended for treatment. During the period from December 1958 to March 1970, only 16 reports of untoward reactions were received by the manufacturer from physicians who used three separate lots of Respiratory B.A.C. products. They called attention to local swelling, soreness, redness and itching at injection sites, systemic effects consisting of elevated temperatures (101–105° F), nausea, diarrhea and rash. These reactions were traced to one lot of dessicated B.A.C. powder utilized in the manufacture of the three lots of the finished product. They occurred mostly in children, were temporary and self-limited, and did not deter the continued use of the product by the reporting physicians. No reports of fatal reactions were received. Controlled or partially controlled studies on long-term safety in humans were not submitted.

d. *Labeling.* The same package insert is used for each of the four Respiratory B.A.C. preparations currently marketed. General recommendations and dosages listed in the package insert were noted in the general findings of the Panel under "Manufacturer's Recommendations and Indications For Use." No information is supplied to serve as a guide for selecting one respiratory product over another. The manufacturer indicates that physicians who make inquiries concerning this question are sent a set of published reprints of the articles listed in the package insert. A review of these articles is contained in the general Panel findings on "Clinical Effectiveness." Detailed examination of these references fails to find specific guidelines for such selection, except to infer that the choice should bear some relationship to infection with, or undue susceptibility to, the bacterial strains listed on the product's label.

Review of submitted data shows that dosage directions are derived strictly empirically based on those often used for immunotherapy procedures with other antigens.

4. *Conclusions*—a. *Critique*—(1) *Composition activity and stability.* The manufacturer has provided data showing that care is taken in the selection and identification of microorganisms which serve as the basis for these products. Some evidence that bacterial antigens in the product retain their stability during the dating period is shown by the gel-diffusion experiment presented by the manufacturer. The more sensitive radioimmunoassays might reveal other antigens, some of which could be important but fail to precipitate with antibodies. No evidence is submitted to support the claim in the package insert that the Boivin antigens or M proteins are present.

(2) *Effectiveness.* Support for effectiveness of these preparations in humans is based entirely on uncontrolled studies, case reports, letters and depositions from physicians and their patients, attesting to favorable results in a wide range of respiratory syndromes associated with infection, allergy, or both. Regarding possible effectiveness based on the long period of each product's use, reference is made to the Panel's position on the extent to which prior use of biologicals can be used to satisfy present standards of safety and effectiveness, as part of their general findings.

(3) *Safety.* Animal data, mainly in mice and rabbits, are presented to show lack of acute or chronic toxicity of these products in equivalent doses many times those recommended for human use. Such data for humans are of extremely limited value. The manufacturer's claim of fewer constitutional reactions compared to standard bacterial vaccines is not well supported, since reactions tend to occur with B.A.C. products as well as with bacterial vaccines in relation to dosage and individual susceptibility. Well-designed comparative studies would be required to

establish the claim that B.A.C. products produce fewer reactions than do killed bacterial cell suspensions.

While the long period of clinical use in humans has shown no overt toxicity, the difficulties in excluding long-term effects in patients treated with these and similar products have been pointed out, as part of the general findings of the Panel.

(4) *Labeling.* The general indications for use of these products stated in the package insert for physician's guidance are extremely broad and involve both the development of protective immunity to bacteria and the reduction in hypersensitivity to bacterial antigens. The present state of knowledge neither proves nor disproves the possibility that bacterial antigens or vaccines in general, or these products in particular, induce either of these effects. Specific indications listed in the insert include illnesses which are not in conformity with standard terminology. The disease states listed required better definition, and their relationship to the bacterial antigens said to be contained in these products should be presented in the context of current medical knowledge.

The present package insert, which is the same for all products, is totally inadequate in guiding the physician-user's selection among the four products marketed. Published articles supplied by the manufacturer, at the specific request of the physician, fail to provide adequate guidance.

b. *Recommendations*—(1) *Respiratory B.A.C.* It is recommended that this product be placed in Category IIIA and that the appropriate license(s) be continued on an interim basis in accordance with the appropriate Federal regulations and recommendations of this report. The reasons for this recommendation are that:

(i) There is no substantial evidence of safety and effectiveness.

(ii) There is presumptive evidence of safety based on published reports and physicians' surveys.

This recommendation to permit continued use of Respiratory B.A.C. during a test period is made on the conditions that no strains of Group A streptococci will be contained in the product in accord with the Panel's statement on the subject as part of their general findings.

In addition, the labeling for this product should state clearly in standard medical terminology the specific indications for use. It should also be stated that local and constitutional reactions occur with this product in relation to the amount given and to the individual patient's susceptibility. The claim that fewer constitutional reactions occur with this product than with standard bacterial vaccine should be deleted, since this has not been determined by adequately controlled studies. Claims that this product induces protective immunity to bacteria and reduced hypersensitivity to bacterial antigens should be omitted until such claims are proven.

Also see "Labeling" statement in this report.

(2) *Pooled Stock B.A.C. #1, Pooled Stock B.A.C. #2, Gram Negative B.A.C.* It is recommended that these three products be placed in Category IIIB, and that the appropriate license(s) be revoked for the following reasons:

(i) There is no substantial evidence of safety or effectiveness.

(ii) There is no evidence presumptive of safety.

The majority of letters from physicians submitted by the manufacturers to support effectiveness and safety refer to Respiratory B.A.C. Hence, most of the safety and, presumably, effectiveness data are based on Respiratory B.A.C. rather than Pooled Stock B.A.C. #1, Pooled Stock B.A.C. #2, and Gram Negative B.A.C.

With reference to the gram-negative organisms contained in both Pooled Stock B.A.C. #2 and Gram Negative B.A.C., there is no evidence presented to substantiate the manufacturer's claim that these products are of benefit to patients with gram-negative infections complicating prolonged treatment with antibiotics. The use of these products would be dangerous if used in lieu of antibiotic therapy.

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STAPHYLOCOCCAL B.A.C. AND POOLED SKIN B.A.C. MANUFACTURED BY HOFFMANN LABORATORIES, INC.

Staphylococci were first described and categorized in the late 1800's when their causal relationship to human disease, particularly skin lesions, was established. Animal studies on the toxic effects of staphylococci suggested that the alpha hemolysin present in culture filtrates was lethal as well as responsible for dermonecrosis (Ref. 1). As the principles of immunology began to evolve, it followed quite logically that attempts should be made to develop methods of immunization against these bacterial toxic properties. Both toxoids and antitoxins therefore came into vogue in the first part of the 20th century, but the clinical results generally were disappointing. In 1928, Alexander Fleming discovered that the mold penicillium had a marked inhibitory effect on staphylococci; this led to the beginning of the antibiotic era a decade later. Thereafter, interest in the use of such vaccines declined, and control of staphylococcal infections by vaccines never became an important aspect of either the prevention or treatment of acute infections.

In the 1940's, Josef Hoffmann prepared several hundred autogenous bacterial antigens from a variety of sources. Initially, these were related entirely to respiratory problems and were made available for clinical testing. By 1958, it became impractical to continue the preparation of autogenous vaccines and, in addition, the Division of Biologics Standards ruled that it would be necessary to settle on a fixed group of bacterial cultures to be used for all future vaccines. Pooled Skin B.A.C. (Bacterial Antigen Complex) and Staphylococcal B.A.C. followed this same general course, although they were developed after the respiratory model had been set. Their distribution began in 1956 and 1958, respectively.

1. *Description*—a. *Composition.* Staphylococcal B.A.C. contains *Staphylococcus aureus*, phage types 42B/52/80/81, and albus in equal proportions. *Staphylococcus albus* is not phage typed in the manufacturer's description. In 1973, two of the original strains were replaced, one because of inadvertent discarding and the other because of the nonviability of the lyophilized stock. The replacements were of similar phage types and other characteristics.

Pooled Skin B.A.C. contains *Staphylococcus aureus* (14 strains) and albus

(2 strains). This includes 9.2 percent phage types 43B/53/80/81 in addition to two strains of *Proteus vulgaris*. The final preparation contains approximately equal contributions from all types.

b. *Preparation.* The Hoffmann B.A.C. products basically are all made in the same way. Standardization is made on the basis of weight, nitrogen content, and appropriate tests for sterility and chemical contamination. Under these conditions, and with the volumes distributed, growth and extraction procedures need to be carried out only once every 5 to 6 years.

2. *Labeling*—a. *Package insert.* A single insert is used for the Staphylococcal B.A.C. and Pooled Skin B.A.C. General comments about B.A.C. preparations are initially made, some of which are not applicable to the staphylococcal or Pooled Skin B.A.C.'s. Emphasis is placed on the acellular nature and on the claim that the Hoffmann products "provide some important antigens lacking in cellular vaccines."

There are three indications:

(1) Staphylococcal and Pooled Skin B.A.C. for treatment of recurrent and chronic staphylococcal infections of the skin, eyes, ears and nose.

(2) Hoffmann B.A.C. products in general are recommended to induce antibody formation in "the chronically ill patient."

(3) Hoffmann B.A.C. products in general are recommended for desensitization of patients known to be allergic to the bacteria represented in the vaccines.

A section on rationale states that "B.A.C. therapy" confers both antitoxic and antibacterial immunity in mice. References are made to an abstract and to an article dealing primarily with Respiratory B.A.C. of which the latter states that patients with chronic lung disease were in many cases improved by the addition of Staphylococcal B.A.C. to the other B.A.C.'s they had been receiving.

Administration is recommended in doses of 0.02 to 0.05 milliliter intradermally and 0.035 to 0.10 milliliter subcutaneously. The intradermal route is suggested for best results. Increments are recommended if the patient fails to sustain improvement. The suggested intervals are weekly for 4 weeks, twice biweekly, and then once monthly throughout the year. Unspecified variations of intervals according to the response of the recipient are advocated. No more than two B.A.C. products at any one visit are suggested, and pooling of B.A.C. products is not considered advisable. No references are given to indicate the basis for these statements.

Standard precautions are listed, and it is stated that if the patient is known or suspected to be hypersensitive to bacterial antigens, the initial dosage should be considerably reduced. Significant side effects are said to be "uncommon," and it is specifically stated that there are no known contraindications to the use of B.A.C. antigens.

b. *Other promotional material.* A limited amount of advertising in medical journals had been placed prior to 1972, but none since then. Hoffmann, Inc., employs no detail men. The bulk of advertising has been in direct mailings to physicians, consisting of reviews of all B.A.C. products and order forms. In 1972, mailings were sent to 53,634 physicians in the United States. The information supplied is essentially identical to that described for the package insert.

The package circular has no therapeutic claims or suggestions.

3. *Analysis*—a. *Theoretical considerations*—(1) *Effectiveness.* The problems of developing a coherent rationale for the use of staphylococcal antigens in staphylococcal disease is largely related to the fact that no one as yet understands why disease is produced. As Morse (Ref. 2) has pointed out,

> The inability to incriminate a single product, component, or property of *Staphylococcus aureus* as the determinant of pathogenicity is a recurring feature in the history of research in staphylococcal disease. Included in the list of substances or characteristics which have been advanced as primary factors are: coagulase; alpha toxin and hemolysins; leukocidin; lipase; hyaluronidase and other enzymes; and the ability of the organisms to resist phagocytosis or to multiply within phagocytic cells. In each instance, proponents have been unable to gather sufficient evidence to establish the role of the proposed mechanisms. Only the ability of staphylococcal enterotoxin to induce food poisoning, but not invasive disease, remains intact in the legacy of this search.

Aside from the problems of relating the various staphylococcal toxins to disease, the role of host resistance in disease is equally difficult to understand. No clear evidence is available to show the relative roles of circulating antibody or immediate or delayed hypersensitivity in either protection or pathogenesis. This confusion is exemplified in the manufacturer's recommendation for use. The products allegedly may work either by increasing resistance and immunity, or by decreasing or increasing a preexisting hypersensitivity. Certainly, analogies for any of these hypotheses can be found in other microbial immunologic systems. For staphylococcal disease, however, it can only be said that no solid theoretical base has been established for any form of immunotherapy. Recent work by Mudd and his associates has clearly shown the development of cell-mediated (Type IV) hypersensitivity to staphylococci (Ref. 3), but the part this plays in disease or resistance is not yet clear.

The "acellular" nature of the bacterial product is considered by the manufacturer to be of considerable importance. Since the role of staphylococcal antigens in general is not understood, it follows that there is no reason to expect any one method of preparation to be superior to any other. On a conceptual basis, a whole bacterial cell antigen might even be preferable to an "acellular" preparation.

It is difficult to devise any theoretical framework for the inclusion of *Proteus species* in Pooled Skin B.A.C.

(2) *Safety.* Theoretical dangers include all those inherent to any product used parenterally, particularly when the type and multiplicity of antigens in the preparation have not been completely identified.

Recommended use as either a desensitizing agent or a stimulator of circulating antibodies also points up theoretical dangers. In contrast to sensitivities such as those to certain pollens, no good way apparently exists to determine levels of preexisting sensitivity to staphylococci or other bacteria. Initial dosages must therefore be considered to possess a potential danger if one accepts the hypothesis that abnormal hypersensitivity is at least partially responsible for the initial disease state. While staphylococcal infections are often related to a type of chronic skin disease, their potential to threaten life under appropriate circumstances is well known. It should be recalled that interest in staphylococcal toxins was prompted in large part by the disaster in Bundaberg, Australia, in 1928, in which more than half of the children who received a diphtheria toxin-antitoxin mixture contaminated with staphylococci developed symptoms in 5 to 7 hours and died within 2 days (Ref. 4).

4. *Conclusions*—a. *Critique*—(1) *Effectiveness*—(i) *Animal studies.* Data showing serologic responses in lower animals are adequately presented, and agar gel precipitation tests using hyperimmune animal sera document antigen antibody reactions. Although such tests may be useful in demonstrating that staphylococcal antigens are present in the product, the ability to stimulate the formation of circulating antibodies in animals is not substantial evidence for effectiveness in human disease.

Antitoxic immunity following B.A.C. immunization, as measured by the prevention of paralysis or limping in mice after inoculation with virulent, staphylococci, has been documented (Ref. 5). In addition, "antibacterial" immunity was observed by noting a decreased rate of recovery of viable staphylococci in immunized mice, as contrasted to the controls. In this set of experiments a "cellular vaccine" was also prepared and included. No protective effect was observed, which forms the basis for the manufacturer's contention that the Hoffmann B.A.C. "coprecipitation" process provides important antigens that are lacking in cellular vaccines. It should be noted that this experiment has been reported only once and that the method of preparation of the "cellular" vaccine was not described at all. More importantly, the experiments reported dealt only with a vaccine prepared by the Hoffmann process from a single organism, *Staphylococcus albus* 42D, a designation used in information submitted by the manufacturer. While it is possible to suggest that results would be generally applicable, the manufacturer has presented no data to show that the vaccines as licensed are capable of producing antitoxic and/or antibacterial immunity in any animal species. This general problem of extrapolation is present throughout the Hoffmann submissions. The manufacturer has made little effort to distinguish the

various products, as if the rationale for use and the effectiveness of a Gram Negative B.A.C. were identical to that of a Respiratory B.A.C.

(ii) *Human studies.* No controlled human trials of the effectiveness of either Staphylococcal B.A.C. or Pooled Skin B.A.C. are presented. Effectiveness data are presented as either published literature summaries of treated cases or unpublished compilations of reports requested by the manufacturer from physicians who have used the products.

Simon and Rinard (Ref. 6) reported on 5 years of experience with all B.A.C.'s in the treatment of chronic lung disease. Over 200 patients were included, but the report does not detail in any way how many of them received staphylococcal or Pooled Skin B.A.C. or what the responses were to these specific products. The only comment is made in the discussion section, and states in its entirety,

> In many cases improvement was accelerated and intensified by the addition of Staphylococcal B.A.C. to the other one or two B.A.C.'s the patient had been receiving.

Using this extraordinarily limited data as a basis for the package insert, inference that Staphylococcal B.A.C. could be of value in chronic lung disease is of dubious judgment at best.

An article on nummular eczema in children (Ref. 7) submitted by the manufacturer states that:

> The addition of staphylococcus toxoid, Staphylococcus B.A.C. (Hoffmann), or Pooled Skin B.A.C. (Hoffmann) to the treatment armamentarium is helpful and may bring about a complete remission of the disease.

No data are presented to support this statement, nor is any reference given to other literature.

Simon and Rinard (Ref. 8) used Staphylococcal B.A.C. as well as the others in clinical treatment and reported improvement, although rates were not presented. The primary purpose of their presentation was to document a complete lack of correlation between skin test reactivity and clinical response to the product.

A series of three submitted papers deal with the release of histamine from whole blood before and after treatment of allergic patients with various vaccines, including a staphylococcal vaccine (Refs. 9 through 11). Histamine release was found to be significantly decreased after vaccine treatment, and this was accompanied by objective evidence of clinical improvement after exposure to the offending antigens such as animal dander and various pollens. Thus a nonspecific beneficial effect of staphylococcal vaccine on general immediate hypersensitivities was suggested. The studies, however, were uncontrolled from the clinical standpoint, and the staphylococcal vaccine was evidently a cellular vaccine unrelated to the Hoffmann products. The data are thus not relevant to the products under review.

A clinical compilation was made from 1,852 patients treated with either Pooled Skin B.A.C. or Staphylococcal B.A.C. (Ref. 5). Compilation results were obtained by a questionnaire survey of physicians in collaboration with the manufacturer. The cases dealt primarily with skin infections, although a variety of eye, ear, nose and throat infection cases also were included. There were reports of 977 cases having "excellent" results, and 610 cases were reported as having "good" results. No objective bases for these criteria were supplied. There were 304 physicians surveyed using an unspecified selection process, of which 109 physicians reported; however, according to the compilation "a number did not supply all the information requested."

In addition to this report, the manufacturer has submitted to the Panel compilations or individual case reports from 306 patients provided by 93 physicians. Physicians who used B.A.C. during the period 1956–1972 were contacted, so this separate submission may have included many of the cases referred to in the previous report published in 1961. Specific response rates are not given. The questionnaire distributed was detailed and included requests for laboratory data and data on frequency of inoculation and length of treatment. It also included an attempt to objectively calibrate responses through use of data concerning frequency of infection, size and number of lesions, duration of illness and necessity for other medications. Overall improvement rates were comparable to those previously reported, i.e., 80 to 90 percent.

The value of such data are limited for several reasons:

(*a*) The data are uncontrolled. As indicated in this review, uncontrolled trials can have value only in circumstances where the natural history of the disease in question is precisely known and is not subject to variations unrelated to the therapeutic agent. Such is not the case with the majority of forms of staphylococcal diseases. Reports of controlled studies of other products have clearly demonstrated the significant improvement that can be seen in placebo treatment cases (Refs. 12 and 13). Reasons for such variability are not completely known but may reflect seasonal variation, a natural decline with aging psychologic factors, or other measures introduced into the treatment situation.

(*b*) In the published series (Ref. 5), only one-third of the physicians answered the questionnaire. The method of approach for the more recent unpublished survey, which was initiated by the manufacturer in response to the request for information on safety and effectiveness of bacterial vaccines and antigens published in the FEDERAL REGISTER of August 18, 1972 (37 FR 16690), was a letter from the manufacturer to physician purchasers of B.A.C. products. This letter enclosed the questionnaire and emphasized the urgency of a reply. The rate of physician response on the use of Staphylococcal B.A.C. and Pooled Skin B.A.C. is not clear, although 38 physicians reported on 151 cases using these two products.

(*c*) Truly objective measures of clinical benefit were not obtained. Virtually all were susceptible to a significant degree of subjective interpretation.

(2) *Safety*—(i) *Animal studies.* Safety in laboratory animals has been more extensively studied for the Hoffmann products than for others of this class. Repetitive inoculations of mice covering spans of over 1 year and extensive autopsy studies have been included. Toxic levels in standard laboratory species appear to be well beyond approachable human dosages, and no overt immunological problems have been seen. It should be noted, however, that humans and lower animals differ markedly in their reactions to staphylococci, and an appropriate model in lower animals does not exist. Thus the animal studies primarily reflect a lack of major toxic phenomena.

(ii) *Human studies.* Review of published literature and data compiled from physician questionnaires reveals no instances of severe reactions. One instance of nausea and vomiting and one of psychosomatic syncope were reported. The remainder of reported reactions were minor side effects of momentary local burning and pain at the site of injection, itching 24 hours after injection, occasional malaise and headache, and occasional febrile reaction.

The questionnaire submitted was relatively detailed and specific. In examining the data, however, the following points should be noted:

(*a*) The source for the selection of physicians solicited has not been explained. Presumably this came from the manufacturer's direct sales records. Thus physicians obtaining the products sporadically through a pharmacy would not have been included.

(*b*) A denominator is not available for the compiled submitted data. It is not stated how many physicians were solicited in order to obtain the 306 case reports from 93 physicians. Judging from the published summary of earlier questionnaire data from 1961 (Ref. 5), only about one-third of the physicians responded with any reports.

(*c*) Of those who returned questionnaires, many probably did not answer the question on side effects. Again, extrapolating from the earlier report, 30 of 109 physicians did not answer side-effect questions.

(*d*) When available, side effect data were indicative of only gross, major reactions. No indication is available to indicate that less easily demonstrable side effects requiring laboratory documentation were sought. Although laboratory data were requested, no information is given of the number of completed responses.

To summarize the safety considerations, neither experimental animal nor human use data have shown significant adverse reactions, nor is there any compelling theoretical reason to expect them. However, the human use data are flawed by problems of bias, and it becomes impossible to derive any meaningful risk estimates. From the information available, severe reactions, possibly life

threatening, could occur at rates of 1:500 to 1:1,000. No information is available on possible kidney, liver or lung damage. No information was provided on the presence or absence of bacteriophage or its residual antigen(s) at any stage in the manufacturing process. The Panel shares the, as yet, theoretical concern about the possible adverse effects of long-term parenterally administered bacteriophage, live or killed (Ref. 14). Thus safety cannot be said to have been substantially demonstrated.

(3) *Labeling.* On the basis of the preceding discussion, it is clear that the package insert and promotional material contain statements that are misleading and not in accord with the weight of scientific evidence. In particular, the material should refer only to the products involved, not the entire gamut of B.A.C. preparations. It should be noted that controlled human trials have not been done. The implication of effectiveness in chronic lung disease should be removed, and reference should be removed to phage typing of *Staphylococcus albus*.

(4) *Benefit-to-risk ratio.* Since benefit has not been substantially demonstrated, the ratio must be low.

Staphylococci, if invasive, can be life threatening. In such circumstances, however, antibiotics would form the basis of treatment. The type of staphylococcal disease for which the vaccines are recommended are chronic nonlife threatening conditions. Some instances of chronic furunculosis or other recurrent staphylococcal infections may occur that are not easily handled by antibiotics. In such relatively rare instances it would be of definite value to have another form of therapy available.

b. *Recommendations*—(1) *Staphylococcal B.A.C.* It is recommended that this product be placed in Category IIIA and that the appropriate license(s) be continued on an interim basis in accordance with the appropriate Federal regulations and recommendations of this report. The reasons for this recommendation are that:

(i) There is no substantial evidence of safety and effectiveness.

(ii) There is presumptive evidence of safety based on published reports and/or physician surveys.

(iii) The rcommendation that Staphylococcal B.A.C. be placed in Category IIIA is contingent upon compliance with the Panel's recommendations for changes in labeling, package insert, and all promotional material to encompass the following concepts:

(*a*) Information should be specific for the individual product Staphylococcal B.A.C.; i.e., the product should be presented separately, not simply as one of many B.A.C. preparations.

(*b*) Implication of effectiveness in chronic lung disease should be omitted.

(*c*) Reference to phage typing Staphylococcus albus should be omitted.

(*d*) See "LABELING" statement, which appears above in this preamble.

(iv) In addition to labeling, package insert and promotional material changes, the manufacturer must provide evidence that the cultures used for the preparation of the product do not contain bacteriophage(s).

(2) *Pooled Skin B.A.C.* It is recommended that the product Pooled Skin B.A.C. be placed in Category IIIB, and the appropriate license(s) be revoked for the following reasons:

(i) There is no substantial evidence of safety and effectiveness.

(ii) There is no evidence presumptive of safety.

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BACTERIAL VACCINE MIXED RESPIRATORY (MRV OR MVRI) MANUFACTURED BY HOLLISTER-STIER, DIVISION OF CUTTER LABORATORIES

1. *Description*—a. *Composition.* This is a mixture of chemically killed organisms, suspended in physiologic saline, and consisting of:

Organisms:	*Millions per cubic centimeter*
Staphylococcus aureus and *albus*	1,200
Streptococcus pyrogenes, viridans and *nonhemolytic*	200
Diplococcus pneumoniae	150
Neisseria catarrhalis	150
Klebsiella pneumoniae	150
Haemophilus influenzae	150
Total	2,000

b. *Preparation.* The package insert states:

The organisms are grown in artificial media suited for rapid growth, washed with physiological salt solution, centrifuged and suspended in salt solution and killed with thimerosal. The suspensions are standardized and mixed in required amounts and filled in rubber-stoppered bottles. The filled bottles are tested for sterility and safety in the approved manner. Thimerosal 1:10,000 is used as a preservative.

It continues,

The vaccine is prepared from many strains of bacterial organisms commonly found in respiratory tract infections. Many of these strains were isolated in preparation of autogenous vaccines for patients subject to respiratory infections. All strains of Group A beta hemolytic streptococci known to be associated with glomerulonephritis or rheumatic fever are excluded from this vaccine.

Further information regarding the source of the organisms used is found in Hollister-Stier's response of January 20, 1970, to a request for more information regarding the vaccine.

The cultures in production bottles are washed and centrifuged with physiologic saline, the organisms are chemically killed with 1:10,000 thimerosal, and then resuspended in physiologic saline with a final concentration of 1:10,000 thimerosal.

Standard tests for sterility of the finished product by culture, and the standard animal safety test inoculating two mice and two guinea pigs, with a 7-day observation period, are done for each bacterial vaccine.

Enumeration for each organism is performed by comparing turbidity with barium sulfate nephelometer standards in a photometer. For each species there is the statement, "Plans in future to enumerate by direct microscopic count on membrane filiters." There is no information that this change has been made in the manufacturing process.

2. *Labeling—Package insert.* The package insert states that:

This vaccine is not designed as a prevention or treatment of the virus "colds." Neither will it give a lasting immunity to the "secondary invaders." It is designed as an aid in the desensitization to the common bacterial organisms present in the respiratory system. Such densitization can best be ac-

complished by subcutaneous injections of small doses, gradually increased and given over a long period of time.

The following is a recommended dose schedule:

Prophylactic: ----	0.05 cc (1 minim).
Increase: ------	0.05 cc to 0.1 cc, (1–2 minims), every 4 to 7 days.
Maximum ------	0.05 to 1.0 cc.

Increasingly large delayed local reactions may occur after administering maintenance doses for many months. Continued administration of vaccine even at smaller doses may continue to increase the reaction. Stop vaccine injections. A rest period of 2 to 6 months may allow the delayed hypersensitivity to subside and the injections may be resumed if still needed by the patient.

Repeat maximum dose at monthly intervals during susceptibility period.

Acute condition---	0.02 cc to 0.05 cc (½ to 1 minim).
Increase -------	0.02 cc to 0.05 cc (½ to 1 minim) 3- to 5-day intervals.

Decreasing the doses by one-half or three-fourths, or discontinuing the vaccine is advised if increasingly large local delayed reactions occur, or the condition under treatment becomes aggravated. "Caution is recommended in administering bacterial vaccine to patients with rheumatoid arthritis, lupus erythematosis or other collagen di-

3. *Analysis*—a. *Description of product.* There is no information to indicate how the stock cultures are maintained. Their sources are various, ranging from strains isolated from patients to ATCC cultures that are not identified by number. The organisms are not tested for virulence, and until a recent proposal by the manufacturer, apparently have not been tested for antigenicity. The presence of media constituents, brain, heart (beef), peptones and agar are noted, and no information is available as to how much of these remain in the finished product.

The package insert states that:

all strains of A Beta hemolytic streptococci known to be associated with glomerulonephritis or rheumatic fever are excluded from this vaccine.

The list of types used includes Types 4, 10 (12) and 18, which are nephritogenic (Ref. 1) and Type 28, which is erythrogenic. All Group A streptococci are capable of initiating infections that culminate in acute rheumatic fever regardless of type.

The question raised regarding the actual bacterial count of the final product seems to be adequately answered and accurate by whatever method is being used—turbidity or direct count. Supplementary information supplied by the manufacturer compares direct counts of stored and new products, showing no change after storage.

b. *Labeling.* An abbreviated dosage schedule is given, presumably for subcutaneous injection, although labeling for intracutaneous injections is also present. The labeling includes an expiration date and a storage temperature of 5°C+ or —3°C.

Other than warning to use separate heat-sterilized tuberculin syringes for each patient and to obtain accurate measurements, no warning is given about possible acute allergic reaction or anaphylaxis, except in a reference in the disclaimer warranty statement "* * * of the inherent danger of injecting any biological product."

The implication on the package insert is that the vaccine is to be used for desensitization, but no specific disease states are listed and no method is suggested for determining whether the patient is sensitive, and to what degree. That there may be differences in patients is implied by the phrase "a treatment set of four graduated dilutions of the vaccine and other bacterial mixtures is available."

The rationale for the selection of the strains used in the vaccine is that they were commonly isolated from patients with respiratory tract infections. The basis for the incorporation of each component is empirical, as are the bases for determining the concentration and dosage (Refs. 2 and 3).

c. *Theoretical considerations*—(1) *Effectiveness.* The possible values of respiratory bacterial vaccine could be: (i) To stimulate immunity to infections, and (ii) to diminish bacterial allergy. The first value is disclaimed by the manufacturer in the package insert, relative to "lasting immunity" in humans. The second possibility is based on the proposition that "sensitivity" to bacteria is the basis for a variety of upper and lower respiratory syndromes characterized by edema, exudates and airway obstruction. There is no clear distinction as to whether this is, by analogy with treatment of proven extrinsic reaginic allergy, a sensitivity of the immediate type, or whether this is delayed hypersensitivity, which is implied as being manifest by large local reactions to the vaccine in the course of its administration, as indicated on the package insert.

The experiments by Kasuga sponsored by the manufacturers, now underway to update the information on the antigenicity of the MRV, include studies of the delayed skin test in sensitive human recipients and of the Macrophage Inhibition Factor (Ref. 23).

Without an animal model or clearly defined target population whose disease is sharply defined, and whose immune capability is known, it is difficult to evaluate the studies that have been reported and to conceive of critical studies that will resolve these basic questions.

The weight of clinical evidence supporting the effectiveness of bacterial vaccines in humans is largely uncontrolled and anecdotal, but it comprises many thousands of patients and its use spans a period of at least 40 years. In this clinical material are some outstanding examples, seemingly distinct from the majority, of individuals who do react differently to bacterial infections and in ways that so closely resemble the animal models of hypersensitivity of various types that one inescapably feels the individuals do have altered reactivity to infection. Unfortunately, our understanding of these reactions and our techniques for investigating them are just emerging; thus, the older studies that have been reported on these patients are difficult to interpret in the light of the little we now understand.

(2) *Potency standards.* To date, the MRV has had as its only measure of potency the enumeration of the number of each species of killed organisms per milliliter. Methods of detecting the presence of these organisms by using a specific precipitating antibody, and possibly of measuring the amount of antigenic material present, are being evolved. Other immunologic tests are being applied to the vaccine, and it is already known to have a well-recognized ability to elicit both immediate, intermediate, delayed and arthus-type skin reactions in human skin. These are but a few of the parameters that should be known in order to ensure a stable, reproducible and biologically active product.

(3) *Safety.* There has been no systematic review of the safety of these vaccines. Theoretically, repeated injections of capsular polysaccharides of invasive bacteria such as pneumococci, *H. influenzae* and *Klebsiella pneumoniae* could exert a suppressive effect upon acquisition of immunity to these organisms (Ref. 4). Further, injection of media components, such as bovine proteins, could produce long-term adverse effects. Also, see Panel statement regarding the Group A streptococcal antigens.

d. *Available data*—(1) *Effectiveness.* A wide divergence of opinions was submitted regarding clinical indications for treatment, use in adults versus children, use of skin tests, etc. There is also a difference of opinion among the reported studies as to the value of bacterial vaccines for the conditions in which they have been used (Refs. 5 through 7).

The weight of human clinical evidence supporting effectiveness is uncontrolled or anecdotal. Documented case reports from 18 physicians were submitted by the manufacturer and include information about 1,134 patients, both adults and children whose ages often are not specified. A summary of these physician reports was developed by the Panel. Ailments treated consist chiefly of asthma, bronchitis, allergic rhinitis, infectious sinusitis, chronic respiratory infection, and also serous otitis media, conjunctivitis, blepharitis, otitis externa, headaches, urticaria and atopic dermatitis. The route of administration often is not specified, but presumably it is by subcutaneous injection, by variable dosage schedules, for varying periods of time. The results are not expressed in uniform or always precise form but are generally reported to be good. Among the 10 physicians indicating improvement expressed in percentages, "good" results were noted in 50 to 100 percent. Others described patients as "immensely improved, etc." Eight physicians reported using MRV along with allergens, dust, mold or histamine in this group of patients.

Clinical impressions are conveyed in responses from among 2,421 customers surveyed in 1971. As submitted by the manufacturer, this yielded 99 letters from physicians (4.09 percent of the customers replying). Seventeen physicians reported tens of thousands of patients treated at sometime with MRV, 11 others stated thousands of patients were under current treatment, 17 physicians indicated use in "many," "several dozen," "hundreds," and "thousands," without specifying exact numbers. Fifty did not give any quantitative data regarding the number of cases treated, and four listed themselves merely as "large users" of vaccine. Of 48 physicians who indicated the number of years in practice, 29 had been practicing more than 20 years, 13 for 10 to 19 years, and 6 for 5 to 8 years. A summary of the contents of these letter reports was prepared by the Panel. Only one physician reported "no data on efficacy." In every other instance, the results are generally in the tenor of "good to excellent" results for patients with the same spectrum of respiratory and skin disorders as in the group of "documented case reports" noted above. Dosage and duration of treatment are as varied as the conditions being treated. There is a notable absence of any reported adverse effects from among these treated patients.

The manufacturer submitted several published reports of double-blind, blind, and uncontrolled clinical studies, using MRV or other bacterial vaccine combinations in treating chiefly allergic and infectious respiratory illness.

Fontana et al. (Ref. 8) reported the results of a 2-year double-blind control study to determine the effectiveness of bacterial vaccine therapy in 30 children with infectious asthma. The vaccine used for this study differed from MRV in concentration (6 billion vs. 2 billion organisms per milliliter in MRV), and contained *Pseudomonas aeruginosa* and *Proteus mirabilis* in addition to *Staphylococcus aureus* and *albus*, *Streptococcus viridans* and *Streptococcus hemolyticus*. MRV contains *Diplococcus pneumoniae*, *Neisseria catarrhalis*, *Klebsiella pneumoniae* and *Haemophilus influenzae*. During the first year of the study, all children received saline injections weekly from October to April, and records were kept of number of days of wheezing, number of infections and number of injections associated with wheezing. In the second year of the study the same observations were continued with patients randomly divided into placebo and vaccine group. A reduction in the incidence of wheezing, infection and infection episodes associated with wheezing was observed in a larger percentage of the placebo group than in the vaccine-treated group. The results of the study are somewhat marred by the following points: (i) of 41 children ages 2–10 years originally entered the study; 11 dropped out who are not accounted for; (ii) the age of the patients was not taken into account in randomizing the individuals, so that two-thirds of the placebo-treated patients were over 9 years of age, and two-thirds of the vaccine-treated were less than 9 years. This could be a very significant difference in the groups since asthma may spontaneously improve in the older child. The authors acknowledge the importance of this difference.

The double-blind study, using a vaccine similar, but not identical, to MRV, of Mueller and Lanz (Ref. 9) describes significant differences in favor of a vaccine-treated group of 14 young children who experienced severe asthma only during infections. This was accompanied by a single-blind study of a larger group of children with infectious asthma, who were treated effectively by vaccine.

Barr et al. (Ref. 10) carried out a double-blind study of 52 adult asthmatics and found a significant difference in favor of the vaccine-treated group in only 1 of 7 variables tested.

The statistical designs of the latter two studies did not satisfactorily randomize the patients.

A fourth double-blind study involving 122 patients was done in France, by Boutin et al. (Ref. 11) using MRV, Stallergenes (Hollister-Stier Licensee in France using essentially the same product as is used in the United States). This study showed a significant difference in favor of the vaccine-treated group for bronchitis and rhinobronchitis, but not for asthma.

Additional studies on the effectiveness of mixed bacterial vaccines have been done using the patient's previous condition as his own control, comparing pre- and post-treatment clinical conditions. One of these studies is that of Bruttman (Ref. 12), who treated 37 allergic patients with MRV used as an intradermal injection into the scapuar region. The dose was 2,000 million organisms per cubic centimeter for adults and 200 million organisms for children, in a series of 12 bi-weekly injections ranging from 0.1 to 0.5 cubic centimeters. Of 30 asthmatics treated, 25 benefited—16 very good and 9 good results—lasting for 2 years. Seven patients with rhinitis all had good results for 2 years.

An unpublished study, Nouvel et al. (Ref. 13), of 50 patients subjected to vaccine treatment of bacterial respiratory conditions from September 1, 1970, to May 31, 1971, was presented by Hollister-Stier, using MRV (Stallergenes). Chronic bronchitis, asthma, recurrent infantile rhinobronchitis, tracheitis and conjunctivitis were treated. Preliminary skin tests to detect sensitivity to concentrated MRV were performed. The type of reaction obtained was not stated. Apparently, five "general incidents" associated with fatigue and fever were seen, with 10 instances of local reactions. Overall, 80 percent good results were obtained, the best being in patients under 20 years of age. In a group of 22 asthmatics, 17 had good results, and of the 17 chronic bronchitis patients, 14 had good results. Treatment was by the intradermal route unless local or necrotic reactions occurred, in which case treatment was administered subcutaneously.

A study by Boutin et al. (Ref. 14) compared intradermal therapy with MRV and subcutaneous treatment with CCB Minet Vaccine in 100 patients, and no difference in results between the 2 treatments was noted in patients with chronic bronchitis as 50 percent of those treated with each vaccine reported improvement. Better results were observed in cases of infectious asthma in children treated with MRV than with CCB vaccine. Twenty-one patients noted local reactions; 15 of them were treated with MRV, given intradermally; and of these, 5 patients also had generalized reactions, the nature of which was not described.

An unpublished survey by Kasuga et al., "Responses to MRV Immunization of Normal Adults" (Ref. 23), concludes, on the basis of a continuing study, that injections of MRV into sensitive recipients result in a decrease in the size of the delayed skin test at 24 hours, that precipitin titers were increased in eight of nine patients tested after MRV inoculation, and that injection of MRV showed an increase in Macrophage Inhibition Factor. A review of the data does not show consistent changes in skin test either for the organism or the patient.

The manufacturer presents as a supplement (June 14, 1974) to his original submission, translations of six papers from Spanish investigators (Refs. 15 through 20), reporting on partially controlled and uncontrolled studies with bacterial vaccines other than MRV, in which it is claimed that support is given for the effectiveness and safety of bacterial vaccines in the treatment of asthma and sinobronchopulmonary ailments.

Although a large number of clinical reports were submitted, they represent an uncritical view of the effectiveness of bacterial vaccines in a variety of conditions. Two double-blind studies did not use this particular product. The one using it (Boutin) does show some effectiveness for bronchitis but not for asthma.

The papers cited in the Panel's review are indicative of the wide difference of opinion on this subject.

(2) *Safety*—(i) *Animal.* The standard animal safety tests are conducted for MRV. There are no long-term studies on the effect of repeated injections in a schedule comparable to the human protocol for treatment.

(ii) *Human.* Since the patients who receive bacterial vaccine often are selected on the basis of skin reactivity, with delayed or immediate skin test response, this may be considered an expected, not an adverse, response to vaccine (Refs. 21 and 22). Thus, skin testing does not contribute evidence for or against safety of the product.

The human safety data are described by the manufacturer as being the accumulation of 35 years of marketing experience, without known side effects, except for local reactions and one reported systemic reaction.

e. *Adequacy of manufacturer's presentation.* The original submission was in-

complete in regard to the description of the product and ambiguous regarding the organisms used. This was clarified in supplementary submissions. A fair representation of the pertinent literature was submitted which is extensive on the subject of bacterial vaccines; however, few studies have been conducted using the product under review.

The study of Kasuga is a step toward investigating the responses to MRV in the immunization of normal adults. Final results from this should be available soon. The next phase should be to make similar investigation of persons "hypersensitive to bacteria of the respiratory tract" if such a group can be defined.

The manufacturer submitted evidence from studies which they conducted that indicated MRV contains antigens to the several bacterial constituents, using Ouchterlony plate identification; however, these studies were not carried out with controls to show lines of identity with known standard cultures of each organism, or with media or serum controls. Whether a sonicated preparation of MRV is the same antigenically as the unsonicated whole bacterial vaccine is a question not answered by the information supplied. The manufacturer proposes to carry out additional studies as indicated in a letter dated June 12, 1974.

f. *Benefit-to-risk.* Precise risk rates of any adverse reactions to a mixed respiratory vaccine cannot be determined because of lack of systematic reporting and controlled trials. The risk of catastrophic immediate reaction must be assumed to be very low since there are no reports of such in the literature, nor has a canvas of physicians' experiences produced any such report, and the manufacturer states no such complaints have been received in the course of 35 years, during which time many millions of doses were administered.

Risk of late, mild or subtle reactions from long-term use are even more difficult to determine for the reasons noted previously. The incidences of skin redness, induration, fever, malaise etc., which are sporadically noted, are generally considered to be indicators of sensitivity to the vaccine, but since they are expected, they are not systematically reported. On theoretical grounds, from experimental studies, purified streptococcal antigens can give rise to antiheart antibodies, pneumococcal polysaccharides can cross-react with blood substances, and gram-negative organisms can produce endotoxins. The potential risks for occurrence of these events from the product as now supplied are not known and should be investigated.

From the long years of clinical use of the vaccine without any of these problems being associated with it, it is unlikely that they will occur in any appreciable degree but their potential must be considered.

The purported benefits that may be derived from MRV may relate to a subpopulation that reacts to bacterial infection with asthma, bronchitis, rhinitis and urticaria.

4. *Conclusions.* It is recommended that this product be placed in Category IIIA and that the appropriate license(s) be continued on an interim basis in accordance with the appropriate Federal regulations and recommendations of this report. The reasons for this recommendation are that:

a. There is no substantial evidence of safety and effectiveness.

b. There is presumptive evidence of safety based on published reports and on physicians' surveys.

c. There is a suggestion of effectiveness in the available literature.

This recommendation is made with the provision that all strains of Group A streptococci be removed from the product in accordance with the Panel's statement on this subject as part of its general findings and that the labeling be revised in accord with the Panel's general recommendation on product labeling.

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BACTERIAL VACCINE DIAGNOSTICS MANUFACTURED BY HOLLISTER-STIER, DIVISION OF CUTTER LABORATORIES

1. *Description.* Three groups of bacterial products are presented together in this submission by Hollister-Stier Laboratories—Bacterial Vaccines Diagnostics, Bacterial Vaccine Special Mixture for Treatment, and Mixed Respiratory Vaccine (MRV). The following description of the Bacterial Vaccine Diagnostics was obtained from the manufacturer's general statement, labels, and the professional price list of January 1976, and was extrapolated from the information on MRV for the organisms common to both products.

The products are described as being suspensions of killed bacterial cells containing 1,000 million cells per cubic centimeter,[1] "suspended in physiologic saline containing a preservative of 0.01 percent thimerosal or 0.4 percent phenol," and are supplied in 2-cc and 5-cc vials for intradermal testing.

LABELED AS BACTERIAL VACCINES FOR INTRADERMAL TESTS, 1,000 MILLION ORGANISMS PER CC[1]

Aerobactor aerogenes
Klebsiella pneumoniae (B. Friedlander)

[1] Strength as shown on labels in original submission to Panel. Listed in the January 1976 manufacturer's brochure as available in concentrations of 2,000 or 5,000 million organisms per cubic centimeter.

Corynebacterium pseudodiphtheriticum
Staphylococcus aureus (Albus)
Streptococcus pyogenes
Streptococcus viridans

LABELED AS ALLERGENIC EXTRACT FOR INTRADERMAL TESTS, 1,000 MILLION ORGANISMS PER CC [1]

Corynebacterium (Propionibacterium) acnes
Neisseria catarrhalis
Proteus vulgaris
Salmonella enteritidis
Salmonella schottmuellori
Streptococcus nonhemolyticus (for intradermal use)
Escherichia coli
Gaffkya tetragena
Haemophilus influenzae
Diplococcus pneumoniae mix
Pseudomonas aeruginosa
Salmonella paratyphi
Salmonella typhosa
Shigella flexneri (paradysenteriae)
Shigella paradysenteriae (type Y)
Streptococcus faecalis
Corynebacterium xerosis

2. *Labeling.* The product labeling includes the statement: Diagnostic Allergenic Extracts, use intradermal 0.02 cc, see enclosed directions. Preservative 0.4 percent phenol (code letter P on vial label) or 0.01 percent Thimerosal with disodium edetate 3 ppm.

No code P appears on any individual label; presumably all contain thimerosal. In the original submission, each bacterial vaccine label indicates 1,000 million organisms per milliliter. The January 1976 price list shows strengths of 2,000 or 5,000 million organisms per cc as the concentrations available. The organisms are labeled as Bacterial Vaccine for intradermal tests or as Allergenic Extracts for intradermal tests. No reason is given for the change in strength. The Panel was not provided with information that the skin-test dose had been changed because of the increased strength.

The dose of all the products is 0.02 cc intradermally. The package insert describes in detail how to perform and read an intradermal test. Readings at 30 minutes, 24 and 48 hours are suggested with no mention of a 6- to 12-hour reading. Local reactions are described, but there is no warning of possible anaphylaxis in the description of systemic reactions or any indication as to when a systemic reaction might occur or how to treat it.

The 30-minute reading of an urticarial wheal and erythema is said to:

> indicate a bacterial atopy but occurs infrequently. The typical reaction is delayed in character, resembles the positive tuberculin type in appearance in 24 to 48 hours. Many allergists agree that while bacterial infections commonly influence asthma and other allergic conditions, skin tests cannot be depended upon to incriminate them as etiologic factors * * *. One should make any desensitizing treatment as specific as possible, bacterial allergy is no exception. Hollister-Stier Laboratories can furnish an individualized desensitizing treatment, made according to the physician's selection on the basis of the test results.

The expiration date, as indicated for the organisms used in MRV, is 18 months from the date of issue or 30 months from the date of manufacture.

3. *Analysis*—a. *Product description.* No information is supplied as to the source or type of the various organisms, how they are grown, by what method they are killed, or whether they are assayed by direct count or by barium sulfate turbidity, except as indicated for those organisms used in MRV.

Current nomenclature is not used for many bacterial species; *Diplococcus pneumoniae* mix does not indicate the types used, and other typable organisms are not identified by types. The sample label does not indicate that organisms are killed.

No information is supplied to indicate the reasons for the designation of some products as bacterial vaccines and others as allergenic extracts. All are labeled for intradermal tests with the exception of *Streptococcus nonhemolyticus*, which is marked for "intradermal use."

b. *Safety.* The standard animal safety test is applied to: each lot of each individual species by injection of maximum tolerated dose, generally 0.5 cc in mice and 5.0 cc in guinea pigs. The strength of the suspension is the strongest normally supplied 5,000,000 organisms per cc. The results on file and available for examination of hundreds of these tests over a period in excess of 25 years shows the components have satisfactorily passed these tests as evidence of safety in the animals tested.

There are no data on human safety for these products except for the organisms used in MRV. No marketing data are supplied for the diagnostic vaccines.

c. *Effectiveness.* No information is presented to indicate that these vaccines are active antigens for skin tests, nor for what specific conditions they are to be used for diagnosis. The manufacturer implies that tests with these diagnostic vaccines can be used as the basis for selection of organisms for desensitization, but in what circumstances and what relationship they bear to vaccine treatment is never clarified. Therefore, the absence of any statement regarding effectiveness is not surprising.

d. *Benefit-risk ratio.* All of the organisms that constitute the diagnostic bacterial vaccines either cause specific disease entities that can be, and are, diagnosed by appropriate microbiological techniques, and not by skin tests, or are nonpathogenic normal inhabitants of the respiratory, gastrointestinal tracts, or skin, for which there is no reason to perform a skin test. No benefit has been demonstrated from these products. There is a potential risk for both immediate and long-term adverse effects from injections of any foreign proteins, and from streptococcal proteins in particular, which have been evaluated as unacceptable except for use in controlled research protocols. The bacterial vaccines from the pathogenic organisms in this group of products have been superseded as therapeutic agents by specific antimicrobial agents. For nonpathogens such as *Corynebacterium pseudodiphtheriticum, Corynebacterium acnes, Corynebacterium xerosis,* and *Gaffkya tetragena,* their role as allergens has not been demonstrated. The benefit-risk ratio is not satisfactory.

4. *Conclusions.* It is recommended that all diagnostic Bacterial Vaccines and Allergenic Extracts be placed in Category II and that the appropriate license(s) be revoked because there is no evidence that skin tests with these products are of use in diagnosis.

BACTERIAL VACCINES FOR TREATMENT, SPECIAL MIXTURES MANUFACTURED BY HOLLISTER-STIER, DIVISION OF CUTTER LABORATORIES

1. *Description.* The product is a suspension of killed bacterial cells containing one or more of the organisms for which the license is held and custom formulated on the physician's prescription. Washed organisms are suspended in physiological saline, killed with 1:10,000 thimersosal, and in the final container are preserved with 0.01 percent thimerosal. There are four graded dilutions:

Dilutions (million-organisms-per-cubic centimeter):	*Vial size (cubic centimeters)*
(a) 2	3.7
(b) 20	3.3
(c) 200	3.3
(d) 2,000	4.7

The inactive ingredients consist of 0.9 percent NaCl and possible trace quantities of beef brain heart infusion, peptones, yeast extract, agar, sheep blood, dextrose and sodium phosphate.

2. *Labeling.* The label suggests an initial dose of 0.05 cc for subcutaneous injection. Whether the vaccine is to be used for testing or for treatment is not stated. The dilutions are clearly marked. The package insert gives clear, readable instructions for administration of the vaccine, with precautions and a suggested dosage schedule for average sensitive patients. Included are suggestions for modification for very sensitive patients. No claim is made that bacterial infection is the etiologic factor for any particular disease. Symptoms "most often attributed to bacterial hypersensitiveness are asthma, rhinitis, urticaria, and some forms of atopic skin manifestations." A statement is made about the role of focal bacterial infections, and when these cannot be eradicated, "autogenous vaccines or stock vaccines containing the organisms usually found in such foci are indicated."

3. *Analysis*—a. *Safety.* Animal safety studies consist of the standard tests required by Federal regulations. In the submission, the vaccines are described as containing from 50,000 to 5 billion organisms per milliliter, and in the animal safety test, it is stated that each lot of each individual species is continually tested by injections of the maximum tolerated dose, generally 0.5 milliliter for mice and 5.0 milliliters in guinea pigs. The strength of the suspension is the strongest normally supplied, i.e., 5 billion organisms per milliliter. Whether this concentration is used in the safety tests for the ingredients of the Special Mixture, or the 2 billion concentration, which is the most concentrated vaccine usually supplied, is not clear. The finished prod-

uct is tested similarly. It is stated that hundreds of these tests over more than 25 years of use have been satisfactory.

Human safety data are derived from 35 years of marketing experience without reported side effects.

b. *Effectiveness.* No information directly related to the effectiveness of Special Mixtures Vaccine is presented.

c. *Benefit-risk ratio.* The information provided was inadequate to prove safety and effectiveness. No comment is made as to selection of patients who might be adversely affected by reactions, nor is there any mention of use of the product during pregnancy or in children.

4. *Conclusions*—a. It is recommended that all bacterial vaccines for treatment, except the eight organisms in MRV, including the non-Group A sterptococci, be placed in Category IIIB and that the appropriate license(s) be revoked for the following reasons:

(1) There is no substantial evidence of safety or effectiveness.

(2) There is no evidence presumptive of safety.

(3) The evidence for human safety as presented is confined to case reports in which MRV is the product used. There is no specific information on any bacterial vaccine from the other organisms.

b. It is recommended that the following eight vaccines which are components of MRV be placed in Category IIIA and that the appropriate license(s) be continued on an interim basis in accordance with the appropriate Federal regulations and recommendations of this report.

Staphylococcus (*aureus* and *albus*)
Streptococcus (*viridans* and nonhemolytic)
Diplococcus pneumoniae
Neisseria catarrhalis
Klebsiella pneumoniae
Haemophilus influenzae

The reasons for this recommendation are that:

(1) There is no substantial evidence of safety and effectiveness.

(2) There is presumptive evidence of safety based on published reports and/or physicians surveys.

(3) There is a suggestion of effectiveness for these components when used in MRV in the available literature.

BACTERIAL VACCINE T–50 MADE FROM STREPTOCOCCUS PYOGENES TYPE L–8, OR BY PRESCRIPTION MANUFACTURED BY HOLLISTER–STIER. DIVISION OF CUTTER LABORATORIES

1. *Description.* The vaccine consists of killed-bacteria suspended in physiologic saline with 1:10,000 thimerosal preservative. The treatment set consists of the following five graduated dilutions in 5-cc vials (expressed in organisms per cc):

1. 500,000,000
2. 50,000,000
3. 5,000,000
4. 500,000
5. 50,000

2. *Labeling.* One representative label indicates that the product contains *Streptococcus pyogenes*, Type L–8; another one, a Special Mixture, is for a product consisting of Types L–8, L–19, L–24, L–39 and L–41, all Group A streptococci. The package insert does not describe the contents specifically as to the type of streptococci used; it merely suggests that not more than five strains be included. Presumably, special mixtures can be prepared from any strains of any group, selected on the basis of skin sensitivity. The insert is entitled "Bacterial Desensitization Therapy in Uveitis." If the attacks of nongranulomatous uveitis do not respond to steroid therapy, "desensitization is indicated."

Treatment is successful in about 70 percent of cases adequately treated. Sensitivity is determined by intradermal testing with various strains of alpha, beta, and gamma streptococci, as outlined by Alan Woods, described in Procedure Manual American Academy of Ophthalmology and Otolaryngology, Uveitis Field Study Committee.

This manual is not generally available, but Woods outlined his skin testing procedure in "Endogenous Uveitis" and in a more recent paper (Refs. 1 and 2).

Intradermal testing is performed with a stock set of 60 strains of hemolytic streptococci consisting of:

	Strains
Alpha streptococci	10
Group A beta streptococci	42
Group B beta streptococci	4
Group C, F and G beta streptococci	(1)
Gamma streptococci	1

[1] 1 strain each.

Tests are inspected at 15 minutes and read for erythema and induration at 48 hours. Any immediate reactions will have no bearing on the final interpretation.

The label states "for subcutaneous injection," while the package insert says that vaccines can be given "intravenously or subcutaneously." Under the technique of desensitization and in the paragraph headed "Caution," the label says, "Injections can be given by intravenous, subcutaneous, or intradermal methods." Dilutions are labeled in this vaccine in reverse order to those of the other special mixture vaccine produced by the manufacturer, i.e., vial No. 1 is the strongest, and vial No. 5 is the weakest concentration. This could cause serious errors if users of both types of vaccines do not notice the difference in nomenclature.

The initial dosage suggested on the label, 0.05 cc of vial No. 5 (50,000 organisms per cc), is contradicted in the package insert where it recommends that a 0.1 cc of vial No. 3 (5 million organisms per cc) be used. The instructions continue,

If the patient shows any suggestion of a local reaction to this dose, No. 4 dilution is used. If there is a focal reaction in the eye, the weakest dilution No. 5 is used. When the dose to which the patient does not react is determined, the amount of succeeding doses is gradually increased (by) 0.1 cc at each injection.

There are instructions given for cutting back the dose if systemic or focal reactions occur in the eye, for continuing treatment for 6 months, for retesting and continuing treatment if the patient is still skin sensitive or discontinuing treatment if insensitive. No comment is made as to whether to continue if uveitis is still present. If uveitis recurs after stopping treatment, desensitization should be resumed.

3. *Analysis*—a. *Safety.* No data were provided for animal or human safety.

b. *Effectiveness.* No source was given for the manufacturer's claim of 70 percent successful treatment.

c. *Benefit-to-risk ratio.* The benefit-to-risk ratio is low.

The product is inadequately described, both as to its preparation and the type of organisms it contains. The labeling is confusing, and the package insert is contradictory regarding administration of the vaccine.

There is some weight of support for this vaccine from its clinical usage in selected cases of uveitis, but the hazards of treatment reactions and the potential sensitization to streptococcal M-proteins are not adequately described in the package insert. The theory that nongranulomatous uveitis is associated with focal infections and bacterial sensitivity—particularly to Group A, beta hemolytic streptococci—was proposed by Woods, who found 80 percent of 198 patients with nongranulomatous uveitis as opposed to 27 percent of 185 patients with granulomatous uveitis to have specific bacterial hypersensitivity. He recommended intravenous vaccine treatment, based on animal studies that showed that repeated intravenous injections of bacterial antigens (nonhemolytic streptococci) produce only a low degree, or none at all, of cutaneous reactivity while inducing high precipitin-agglutinin titers (Ref. 3.) He assumed that the intravenous route had little danger of increasing sensitivity, but that it had good chances of desensitizing and possibly immunizing patients.

There were 86 patients with nongranulomatous uveitis and with specific streptococcal sensitivity treated by intravenous desensitization; 67 (78 percent) had either complete cessation of attacks or marked decreases in their frequency and intensity. Twenty-two percent were failures, with some developing transient ocular inflammation who had to be removed from the study. In cases successfully treated and retested, there was practically complete abolition of previous hypersensitivity. In 15 percent with recurrences, there was coincidental reappearance of streptococcal hypersensitivity (Ref. 1).

The high incidence of positive skin tests to streptococcal vaccine, in nongranulomatous uveitis compared to granulomatous uveitis, is not confirmed by Van Metre, who found 67 of 110 patients with nongranulomatous uveitis to have delayed skin reactions to streptococci, and reactions of equal severity and frequency in 244 of 446 patients with other uveal disease (Refs. 4 and 5). He states,

There is no doubt that a given case of uveitis may improve and recurrent attacks cease while the patient is taking the vaccine,

but he said a controlled study of effectiveness is needed and had not been done.

Current investigations and clinical studies of uveitis do not mention streptococcal vaccine therapy, but do concern themselves with cellular immunity, prostaglandins, the apparent increased association of HLA–W 27 genes with uveitis and ankylosing spondylitis, as well as the separate roles of herpes, and adenovirus infections and multiple sclerosis (Ref. 6).

4. *Conclusions.* It is recommended that this product be placed in Category II and that the appropriate license(s) be revoked because there are compelling reasons to assume a lack of safety and an unsatisfactory benefit-risk ratio for this product.

a. In keeping with the Panel's statement regarding the use of Group A streptococcal strains and their derivatives, this product is considered hazardous because it consists of one or more strains of Group A streptococci.

b. Reported studies include instances of local ocular and acute systemic reactions to the intravenous vaccine.

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STAPHYLOCOCCUS TOXOID SCLAVO MANUFACTURED BY INSTITUTO SIEROTERAPICO VACCINOGENO TOSCANO "SCLAVO"

1. *Description.* The toxoid is prepared by formalin treatment of a *Staphylococcus aureus* filtrate. The Wood 46 strain is grown in a liquid medium "composed by meat soaking and tryptic digestion of meat." The 9-day culture is filtered and the filtrate detoxified with 0.2 to 0.4 percent formalin after it has been tested for toxic and antigenic potency. Thimerosal is added as a preservative (0.01 percent) just after detoxification. The product is then tested for general safety in guinea pigs and mice, and for dermonecrosis in rabbits. Rabbits and guinea pigs also are used to test for antigenic potency. The product is also tested for in vitro hemolytic activity.

The finished product is prepared by dilution to a concentration of five combining units. A combining unit is the amount of toxoid bound by one unit of a reference antitoxin distributed by the World Health Organization and measured in milliliters. At this dilution, formalin is "undetectable." It is marketed as a 5-milliliter multiple-dose vial and also as single-dose ampoules containing 0.1, 0.25, 0.5, 1.0 and 1.5 milliliters, usually supplied in a treatment set of eight.

2. *Labeling.* The product is indicated for the prophylaxis of recurrent infections caused by staphylococci and in treatment preferably in conjunction with with antibacterial agents. It is contraindicated in the presence of febrile disease or "cardiovascular, renal, hepatic and severe pulmonary involvement." The action of the toxoid, as described in the package insert, is to produce a specific antitoxin and to exert a desensitizing effect.

Specific directions for administration are provided in the package insert, including the precautionary intradermal injection of the first dose to identify preexisting allergic sensitivity. An appropriate warning regarding possible adverse reactions is included.

3. *Analysis.* At the turn of the century, staphylococcal filtrates were shown to produce lethal, dermonecrotic, leucocidal, hemolytic, coagulation and fibrinolytic reactions, which were attributed to various "toxins." Some were shown to be immunogenic (Ref. 1). Interest in such "toxins" languished until the disaster which occurred in Bundaberg, Australia, in 1928. More than half of the children who received a diphtheria toxin-antitoxin mixture contaminated with staphylococci developed symptoms in 5 to 7 hours and died within 2 days (Ref. 2). This led to extensive research by Burnet, who reported on the production of antitoxic immunity in rabbits in 1929 (Ref. 3). He used the Wood strain of staphylococcus primarily because it could be readily identified with a specific bacteriophage. It also produced a potent, killing toxin. For immunization, he developed an "anatoxin" (toxoid) by formalin treatment of toxin; his method for toxoid preparation has since been used with little modification. He also introduced his unitarian concept at this time, arguing that the various toxic effects were produced by the same immunogenic substance. Rapid development followed in several countries, and favorable clinical reports on the use of toxoid for human staphylococcal infections began to appear in the early 1930's (Ref. 4). Enthusiasm in some quarters for such treatment was bolstered by: (1) Poor understanding of the mechanisms of staphylococcal immunity, coupled with unwarranted acceptance of the diphtheria antitoxin analogy; (2) unquestioned potency of toxoid in stimulating antitoxic immunity in animals; and (3) development of a simple antihemolysin assay that showed a measurable antibody response to alpha toxoid in man (Ref. 5). Thus, the presumed potency of the toxoid was used to encourage uncontrolled clinical studies, despite the lack of substantial evidence that antitoxin has much of a protective effect against staphylococcal infection. For example, rabbit survival was prolonged, but the development of abscesses was not prevented (Ref. 6). Rabbit experiments offer little value in support for human effectiveness since the alpha toxin has biological effects in rabbits (leukocidal and hemolytic) that have not been demonstrated in man. The alpha toxins role in the virulence of staphylococci in man appear to be minor. Treatment of human infection with passively administered antitoxin was of little or no value and was quickly replaced by penicillin when it became available (Ref. 6).

Because of its demonstrated potency as an immunogen and its apparent safety, supported by adequately designed and regulated acute toxicity tests, many investigators assumed toxoid to be effective despite the lack of any well-controlled clinical studies and the appearance of a negative uncontrolled study in the 1930's (Ref. 7). After Burnet's early work, more than two decades passed before any placebo-controlled studies were carried out. Two reports favorable to toxoid have been reported; one was published in 1951 (Ref. 8) and the other was an unpublished report to the World Health Organization submitted in 1962. Both used toxoid prepared by the Wellcome Research Laboratories. The first study involved treatment of Royal Air Force apprentices with pustular acne, recurrent boils and styes. Of 75 subjects, 66 had pustular acne. Of the latter, 34 received toxoid and 32 received a placebo. Two to 3 months after treatment, the difference in degree of improvement favored the treated group, but was not statistically significant. At 6 months, 21 of the toxoid-treated group were improved, but only 5 of the controls; and the difference was highly significant. None was completely cured. A flaw in the study design existed in that only two identifying symbols were used: one for toxoid and one for placebo. Reactions to toxoid soon effectively "broke the code." In addition, most of the organisms cultured from the lesions were coagulase-negative staphylococci.

The second study was conducted by the Statens Seruminstitut in Copenhagen (Ref. 9). Patients with furunculosis were divided into four groups of about 70 each. Treatments were autogenous or stock staphylococcus vaccines, or toxoid. *E. coli* vaccine was given to the control group. After 12 months, 16 of 69 (23 percent) of the control group remained free from relapse, compared with 30 of 70 (43 percent) of those treated with toxoid. The difference was significant at the 5 percent level but not as significant as that with the group treated with autogenous vaccine (57 percent, $p=0.001$). The effect of the stock vaccine was no different from the control vaccine. Since toxoid was given intramuscularly and the others subcutaneously, it would appear that this was a single-blind study.

Very little has appeared in the literature in recent years that can be related to an assessment of toxoid. In 1961, Thal and Egner reported that alpha toxin has a significant toxic action on smooth muscle cells in experimental animals (Ref. 10), but this work apparently has not led to any clinical applications. The only significant work published recently has been with leucocidin toxoid (Ref. 11).

One can speculate that continuing interest in leucocidin reflects the impression that this toxin is more likely than alpha toxin to contribute to the pathogenicity of the staphylococcus, an impression that had its origins in the work of Panton and Valentine more than 40 years ago (Ref. 12), but has never been proven.

a. *Effectiveness.* The company submitted summaries of two clinical studies utilizing its product. The first was a report of 15 cases of chronic osteomyelitis treated both with toxoid and surgery. Seven cases recovered and two showed fair improvement. One had a severe reaction after the second injection (Ref. 13). No mention was made of controls. The second study involved the prophylactic use of toxoid in 106 pregnant women who were treated 1 month before delivery. One case of mastitis occurred in this group. In 99 untreated control subjects, 15 cases occurred. A significant elevation in circulating antitoxin was found in the treated group (Ref. 14). In a detailed review article, also submitted by the company, D'Antona makes many comments about the effectiveness of the toxoid, such as a statement that toxoid is a "sovereign method for radically and definitely conquering the staphylococcal disease, with a percentage of cures exceeding 90 percent" (Ref. 15, p. 17 of translation). Unfortunately, none of these reports cites specific data in support of effectiveness. The company did make available to the Panel the report of the controlled study contracted by the Statens Seruminstitut in Copenhagen described previously (Ref. 9) in which Wellcome, rather than Sclavo, toxoid was used.

b. *Safety.* Animal tests conform to tentative requirements for staphylococcus toxoids (Ref. 16), as well as the standard safety regulations. No information is available on possible long-term adverse effects in animals.

Human safety data is limited to short-term observations in published studies and the general impression of safety (and the self-limited nature of the occasional expected acute adverse reaction) gained from decades of use (Ref. 15). The company reported on its marketing experience from 1949 to 1972, with no complaints except for 37 cases of severe local reactions (necrosis) from the first test dose (intracutaneous). No information on long-term safety exists, except for the usual lack of evidence to the contrary over decades of clinical use. No information was provided on the presence or absence of bacteriophage or its residual antigen(s) at any stage in the manufacturing process. The concern of the Panel regarding possible long-term adverse effects of injecting bacteriophage is discussed earlier in this preamble, under the heading "Safety of Bacterial Vaccines and Products."

c. *Labeling.* The external label specified intramuscular use, while the package insert indicates intramuscular or subcutaneous use. A paper (Ref. 15) states that the subcutaneous route is generally preferred. Thus the label appears to be inconsistent with other information regarding route of administration.

The package insert separates the statement on action (production of antitoxin and desensitization) from that on indications, but the implication remains that such action is related to effectiveness, an association that has not been proven. The recommended use for treatment of active infection is inappropriate and must be removed despite the disclaimer regarding combined treatment with antibacterial agents.

Information on the specific components of the culture medium should be provided.

4. *Conclusions.* It is recommended that this product be placed in Category IIIA and that the appropriate license(s) be continued on an interim basis in accordance with the appropriate Federal regulations and recommendations of this report. The reasons for this recommendation are these:

a. There is no substantial evidence of safety and effectiveness.

b. There is presumptive evidence of safety based on published reports.

c. There is a suggestion of effectiveness in the available literature.

The manufacturing process makes the presence of live bacteriophage in the final product highly unlikely. Nevertheless, the manufacturer must provide direct evidence that this is, in fact, the case.

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STAPHYLOCOCCUS TOXOID; FORMALINIZED: DILUTION NO. 1, DILUTION NO. 2; AND DIGEST-MODIFIED MANUFACTURED BY LEDERLE LABORATORIES DIVISION

1. *Description*—a. *Composition.* Formalinized staphylococcus toxoid is prepared from three strains of mannite and coagulase-positive *Staphylococcus aureus:*

(1) Wood No. 46, phage type 42D.
(2) S80, Phage type 3A/3B/39/55.
(3) 24 m.a., phage type 42D.

b. *Preparation.* The organisms are grown from lyophilized seed cultures in a liquid nutrient medium containing veal infusion and an acid hydrolysate of casein. The organisms are then removed by filtration and the filtrates tested for dermonecrotic potency in rabbits and for hemolytic activity. The toxin is inactivated with 0.3 percet formalin, toxoids are pooled (2/3 Wood No. 46), and the pool tested for sterility, detoxification (hemolytic and dermonecrotic), and general safety. The finished products are then diluted with physiologic saline containing 0.5 percent Bacto protone to contain 100 original dermonecrotic units/cc (No. i) or 1,000 units/cc (No. ii).

Digest-modified toxoid is derived from the Wood No. 46 strain alone, which is grown in an infusion-free medium containing an enzymatic digest of casein. The culture filtrate is digested with refined pepsin and tested for safety, etc., as described above. The final concentration is 10,000 original dermonecrotic units/cc.

c. *Potency.* Potency of the toxoids is tested by immunizing rabbits (with formalinized) or guinea pigs (with digest-modified) for antihemolysin production. No reason is given for using different test species for the two products.

2. *Labeling.* The toxoid is suggested for prophylaxis or adjunctive treatment of recurrent boils, carbuncles, styes and pustular acne. The course of treatment with digest-modified toxoid is somewhat simpler than with the other product, possibly because it produces fewer reactions in man (Ref. 1).

3. *Analysis.* As early as the turn of the century, staphylococcal filtrates were known to produce lethal, dermonecrotic, leukocidal, hemolytic, coagulase and fibrinolytic reactions, which were attributed to various "toxins." Some were

shown to be immunogenic (Ref. 2). Interest in such "toxins" languished until a disaster occurred in Bundaberg, Australia, in 1928. More than half of the children who received a diphtheria toxin-antitoxin mixture contaminated with staphylococcus developed symptoms in 5 to 7 hours and died within 2 days (Ref. 3). This led to extensive research by Burnet, who reported on the production of antitoxic immunity in rabbits, in 1929 (Ref. 4). He used the Wood strain of staphylococcus primarily because it could be readily identified with a specific bacteriophage. It also produced a potent, killing toxin. For immunization, he developed an "anatoxin" (toxoid) by formalin treatment of the toxin; his method for toxoid preparation has been used with little modification ever since. He also introduced his unitarian concept at this time, arguing that the various toxic effects were produced by the same immunogenic substance. Rapid development followed in several countries, and favorable clinical reports on the use of toxoid for human staphylococcal infections began to appear in the early 1930's (Ref. 5). Enthusiasm in some quarters for such treatment was bolstered by: (1) Poor understanding of the mechanisms of staphylococcal immunity, coupled with unwarranted acceptance of the diphtheria antitoxin analogy; (2) unquestioned potency of toxoid in stimulating antitoxic immunity in animals; (3) development of a simple antihemolysin assay that showed a measurable antibody response to alpha toxoid in man (Ref. 6). Thus, the demonstrated potency of the toxoid was used to encourage uncontrolled clinical studies, despite the lack of any substantial evidence that antitoxin had much of a protective effect against staphylococcal infections per se. For example, rabbit survival might be prolonged, but the development of abscesses was not prevented (Ref. 7). Rabbit experiments have little value anyway in support of human effectiveness since the alpha toxin has biological effects in rabbits (leukocidal, hemolytic) that have not been demonstrated in man. Its role in virulence of staphylococci appeared to be minor; treatment of human infections with passively administered antitoxin was of little or no value and was quickly replaced by penicillin when it became available (Ref. 7).

Because of its demonstrated potency as an immunogen and its apparent safety, supported by adequately designed and regulated acute toxicity tests, many investigators assumed toxoid to be useful despite the lack of any well-controlled clinical studies and the appearance of some negative uncontrolled studies in the 1930's (Ref. 8). More than 2 decades would pass, after Burnet's early work, before any placebo-controlled studies were carried out. Two reports favorable to toxoid have been reported, one published in 1951 (Ref. 9) and an unpublished report to the World Health Organization in 1962. Both of these studies used toxoid prepared by the Wellcome Research Laboratories. The first involved treatment of Royal Air Force apprentices with pustular acne, recurrent boils and styes. Of 75 subjects, 66 had pustular acne, of whom 34 received toxoid and 32 received a placebo. Within 2 to 3 months after treatment, the difference in degree of improvement favored the treated group but was not statistically significant. At 6 months, 21 of the toxoid-treated group were improved—but only 5 of the controls, and this difference was highly significant. None was completely cured. There was a flaw in the study design. Only two identifying symbols were used: one for toxoid, another for placebo. Reactions to toxoid soon effectively "broke the code." Incidentally, most of the organisms cultured from the lesions were coagulase-negative staphylococci.

The second study was conducted by the Statens Seruminstitut in Copenhagen (Ref. 10). Patients with furunculosis were divided into 4 groups of about 70 each. Treatment was autogenous vaccine, stock vaccine, or toxoid. *E. Coli* vaccine was given to the controls. After 12 months, 16 of 69 (23 percent) of the control group remained free from relapse, compared with 30 of 70 (43 percent) of the group treated with toxoid. The difference was significant at the 5-percent level, but not as significant as that with the group treated with autogeneous vaccine (57 percent, $p=0.001$). The effect of the stock vaccine was no different from the control vaccine. Since toxoid was given intramuscularly and the others subcutaneously, it would appear that this was a single-blind study.

Very little has appeared in the literature in recent years which can be related to an assessment of toxoid. In 1961, Thal and Egner reported that alpha toxin had a significant toxic action on smooth muscle cells in experimental animals (Ref. 11), but this work apparently has not led to any clinical applications. The only significant work published recently has been with leukocidin toxoid (Ref. 12). One can only speculate that continuing interest in leukocidin reflects the impression that this toxin is more likely than alpha toxin to contribute to the pathogenicity of the staphylococcus, an impression that had its origins in the work of Panton and Valentine more than 40 years ago (Ref. 13), but has never been proven.

a. *Effectiveness.* Lederle toxoids per se have not been proven effective by properly controlled studies. The one controlled study using the Lederle toxoid, of which the Panel is aware, was conducted on 601 subjects in an institution for the mentally retarded (Ref. 14). No significant difference from controls was observed relative to occurrence of staphylococcal infections. However, the study was not properly controlled, as it was not "blind" and the control subjects were not placebo-treated. Furthermore, poor hygiene was common in this population; and recurrent staphylococcal infections occurred at a high rate, related directly to the degree of mental deficiency. Thus, a possible beneficial effect of the toxoid might have been masked.

The company submitted several published reports. An uncontrolled study by Dolman (Ref. 5) described the treatment of 28 patients with salutary results associated with increased titers of circulating antitoxin. A similarly conducted uncontrolled study was described by Parish, O'Meara and Clark, 1934 (Ref. 6). In 1935, Murray reported improvement or recovery in 107 of 116 patients with a variety of staphylococcal infections (Ref. 15). The only comparison made was with 100 normal subjects in whom antitoxin blood levels were not significantly different from pretreatment levels of the patients. A 2-year study by Dolman (Ref. 16) involved 306 patients treated for a variety of localized staphylococcal infections. Eighty-one patients with recurrent furunculosis were described as having excellent responses to therapy. In 59 patients with subacute to chronic osteomyelitis and 42 with acne vulgaris the results following toxoid therapy were described as encouraging. Reactions were noted as rarely being troublesome. Other uncontrolled studies included treatment of staphylococcal skin lesions (Ref. 17), correlation of antihemolysin titer with toxoid treatment in chronic osteomyelitis (Ref. 18) and treatment of impetigo (Ref. 19). The one partially controlled study submitted by the company is described earlier (Ref. 14). Only one published report stated that Lederle toxoid had been used (Ref. 18).

b. *Safety.* Animal tests conform to tentative requirements for staphylococcus toxoids (Ref. 22), as well as the standard safety regulations.

Human safety data is limited to short-term observations in controlled and uncontrolled studies and seems adequate. The use of veal infusion in the preparation of the standard toxoid (but not the digest-modified) raises the possibility of sensitizing individuals to bovine antigens or inducing allergic reactions in those previously sensitized, even though no reference is made to such a hazard in one recent monograph on the subject (Ref. 20). No information on long-term safety exists, except for the usual lack of evidence to the contrary during decades of use by physicians. The company received 10 complaints over a period of almost 8 years, of which 5 were probably related to the toxoid treatment itself: acute local reactions, urticaria, anaphylaxis. During 3 of these years, toxoid was administered by physicians approximately 800,000 times, according to the National Disease and Therapeutic Index. How much of this was Lederle toxoid was not recorded. No information was provided on the presence or absence of bacteriophage or its residual antigen(s) at any stage in the manufacturing process. The concern of the Panel regarding possible long-term adverse effects of injecting bacteriophage is discussed earlier in this preamble, under the heading "Safety of Bacterial Vaccines and Products."

c. *Labeling.* The following claims are in the package insert for formalinized toxoid.

(a) Beneficial effects of staphylococcus toxoid therapy, can, to a great extent, be measured by antitoxin production.

(b) In many instances, desensitization is in no small measure responsible for success in treatment.

In fact, there is no good correlation between antitoxin levels in the serum and disease activity (Ref. 21), and the second statement is not supported by any objective data. The additional statement that "not infrequently the best results have been obtained in persons who evidenced marked sensitivity" is unsubstantiated. The digest-modified toxoid, for which no such claims are made, is recommended by implication for such patients because its "allergenic" quality is modified, and it is thus safer to use.

The recommended treatment schedules were designed primarily to minimize acute adverse reactions.

4. *Conclusions.* It is recommended that this product be placed in Category IIIA and that the appropriate license(s) be continued on an interim basis in accordance with the appropriate Federal regulations and recommendations of this report. The reasons for this recommendation are these:

a. There is no substantial evidence of safety and effectiveness.

b. There is presumptive evidence of safety based on published reports.

c. There is a suggestion of effectiveness in the available literature.

This recommendation is made with the stipulation that veal infusion broth may no longer be used in the manufacturing process. Although this process makes the presence of live bacteriophage in the final product highly unlikely, the manufacturer must provide direct evidence that this is, in fact, the case.

Furthermore, the package insert should not include the statement associating beneficial effects with antitoxin production or the implication regarding desensitization until substantial evidence for such claims is obtained.

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IMMUNOVAC ORAL VACCINE TABLETS (BIO. 2155) MANUFACTURED BY PARKE, DAVIS AND COMPANY

For the two decades following the influenza pandemic of 1919, extensive efforts were made to develop effective vaccines against serious infections from various respiratory pathogens. These efforts were extended to include preventive treatment of the milder recurrent bacterial complications of the common cold. Because of the impression that any vaccine effect would be shortlived, and that frequent injections would be costly, time-consuming, and unlikely to be generally accepted by patients, research on oral vaccines was instituted in animals, which yielded promising results. In addition to inducing antibody production, vaccines had a protective effect under certain conditions. In one of the last studies reported, a slightly different formulation of oral vaccine protected rats from fatal doses of pneumococcus Type I; the recommended human dose was used (Ref. 1 below).

Proponents of oral "cold" vaccines recognized the problem of developing a polyvalent vaccine that would impart immunity to the numerous species of bacteria that might complicate respiratory viral infections. Rockwell and VanKirk attempted to get around this problem by selecting organisms with high contents of heterophile antigens which might stimulate much broader immunity than would species-specific antigens (Ref. 2). They observed that heterophile antibody production could be induced by oral vaccine and reported some correlation between antibody titer and clinical improvement (Ref. 3).

1. *Description* — a. *Composition.* Immunovac Oral Vaccine contains the following bacteria which are provided in enteric-coated tablets (numbers in billions of organisms per dose):

(1) *D. pneumoniae*	
Type I–10	
Type II–10	
Types III, V, VII, VIII and XIV—each	
Total	30.0
(2) Streptococcus (½ beta hemolytic, ½ alpha)	15.0
(3) Staphylococcus (½ aureus, ½ albus)	3.0
(4) *N. catarrhalis*	2.5
(5) *H. influenzae*	2.5
(6) *K. pneumoniae*	1.0
(7) Diphtheroides	1.0

b. *Preparation.* The above organisms are killed with cresol, centrifuged and resuspended in saline. In addition, "immunogens" are added. These are the centrifugates of cultures containing 2 billion organisms per dose of each of the above except *k.* pneumoniae and diphabove except K. *pneumoniae* and diphtheroides. The mixture of organisms and immunogens is lyophilized, blended with carrier substances and compressed into tablets.

2. *Labeling.* The package insert states that the vaccine "is indicated when it is desired to attempt prophylaxis against the species and types of bacteria" contained in the vaccine. Nothing is said about prevention of any particular disease.

3. *Analysis*—a. *Effectiveness.* No information was provided by the manufacturer, nor does any exist in the medical literature regarding the effectiveness of this product. It is tested for potency by mouse protection against *D. pneumoniae.*

b. *Safety.* The manufacturer reported one consumer complaint during a 5-year period. Other than the usual tests for general safety required by Federal regulations, no other information is available.

c. *Labeling.* The labeling is noncommital: No specific indications are given for its use.

4. *Conclusions.* It is recommended that this product be placed in Category IIIB and that the appropriate license(s) be revoked for the following reasons:

a. There is no substantial evidence of safety and effectiveness.

b. There is no evidence of presumptive safety.

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IMMUNOVAC RESPIRATORY VACCINE (BIO. 616); N. CATARRHALIS IMMUNOGEN (COMBINED) (BIO. 340); AND N. CATARRHALIS VACCINE (COMBINED) (BIO. 615) MANUFACTURED BY PARKE, DAVIS AND CO.

1. *Description.* The three products are considered together because they are presented as one submission by the manufacturer and because they are several combinations of many of the same chemically killed bacteria, or sterile filtrates of these cultures mixed to include different concentrations of organisms. The Immunogens(R) are a patented trademark for material said to contain "ectoantigens," which is obtained from live organisms grown on solid media by washing with 0.9 percent saline followed by rapid centrifugation to remove bacterial cells which "prevents formation of bacterial autolysates."

The Immunogens are said to contain the soluble surface antigens of: *N. catarrhalis, D. pneumoniae, H. influenzae,* streptococci, hemolytic and nonhemolytic and staphylococci. All are grown on solid calf serum agar except pneumococci which are grown on rabbit blood agar, and *H. influenzae,* which is grown on chocolate agar. The centrifuged saline suspensions are sterilized chemically and by membrane filtration to remove bacterial cells. The vaccines are all chemically-killed organisms using cresol 0.75 percent.

N. Catarrhalis vaccine (combined) has twice the bacterial count of Immunovac Respiratory vaccine, and both contain *C. diphtheroid and K. pneumoniae.* Immunovac Respiratory also contains Immunogens(R) of all the other organisms which are used in the vaccine, namely *N. catarrhalis,* pneumococci, *H. influenzae,* streptococci and staphylococci. *N. Catarrhalis* Immunogen is twice the concentration of the Immunogens(R) used in Immunovac Respiratory vaccine (parenteral).

All formulations are checked for final sterility with methods not described by the manufacturer.

2. *Labeling.* Each product is separately labeled, with brief descriptions of the manufacturing process, organisms and their concentrates. Indications are slightly different for each one, although all are suggested for prophylaxis and treatment of infections of the respiratory tract. For all preparations daily doses are suggested for treatment. Prophylactic treatment with doses of 0.1 cc subcutaneously (0.25 cc for *N. catarrhalis* vaccine) every 48 to 72 hours is advised. *N. Catarrhalis* Immunogen and Immunovac Respiratory vaccine may be started with 0.2 cc intramuscularly. A schedule of 4 to 8 prophylactic or therapeutic doses is recommended.

Only for Immunovac Respiratory vaccine and *N. Catarrhalis* Immunogen is there any description of reactions, which are local; it is stated that "general systemic reactions are unusual." For *N. catarrhalis* vaccine, it is stated that "It is especially desirable in treatment to maintain the dosage at a level that will not give rise to marked local or general reactions."

3. *Analysis*—a. *Effectiveness.* No information was provided except a few letters chiefly from the patients of 1 physician and references to 2 papers reporting favorable results with the use of a cold vaccine for prophylactic immunization for catarrhal illness and colds in 950 and 500 industrial employees.

b. *Safety.* General safety tests are performed as required by Federal regulations. No reactions were reported by the manufacturer for the period from 1968 to 1972.

c. *Benefit-risk ratio.* The benefit-risk ratio for these three products is low.

4. *Conclusions.* It is recommended that these products be placed in Category IIIB and that the appropriate license(s) for Immunovac Respiratory vaccine (Bio. 616); *N. Catarrhalis* Immunogen (combined) (Bio. 340); and *N. Catarrhalis* vaccine (combined) (Bio. 615) be revoked for the following reasons:

a. There is no substantial evidence of safety or effectiveness.

b. There is no evidence presumptive of safety.

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MIXED INFECTION PHYLACOGEN (BIO. 596) MANUFACTURED BY PARKE, DAVIS AND COMPANY

1. *Description.* Phylacogen is a formulation of modified bacterial antigens, licensed by the manufacturer as Immunogens.® This is a registered trademark for material said to contain "ecto-antigens," which are soluble surface antigens of the organisms used. These "ecto-antigens" are obtained from live organisms grown on solid media, by washing with saline, treating chemically with phenol, and centrifugating to remove bacterial cells which "prevents formation of bacterial autolysates."

Phylacogen is composed of microorganism cultures grown separately, extracted, chemically treated and concentrated in vacuo. The residual mass of organisms and precipitated proteins are removed by filtration. Each milliliter of bacteria-free filtrate is derived from approximately 1,000 million organisms in the following proportions:

a. Streptococcus, hemolytic and nonhemolytic (equal parts)—40 percent.

b. *Staphylococci* (*albus* and *aureus*) (equal parts)—20 percent.

c. *Coli bacilli*—20 percent.

d. Pneumococci, Types 1, 2, 3, 5, 7, 8 and 14 (equal parts)—20 percent.

The organisms are grown on solid medium (calf serum agar) except for pneumococci which are cultivated on rabbit blood agar. The final sterility check with standard methods is not described.

Phylacogen is not marketed in the United States or Canada, and the description submitted for the product is a translation from the Spanish. The label is in Spanish.

2. *Labeling.* This vaccine is meant to be injected either subcutaneously or intravenously, but the first dose should be subcutaneous to determine "the patient's tolerance." The initial dose "should never be injected intravenously. Each dose should be injected at different sites." An initial dose of 1 or 2 milliliters should be repeated daily with increases of from 1 to 2 milliliters "in each dose according to the physical and nervous state of the patient, etc." "Very seldom is it necessary to give the patient more than 10 milliliters subcutaneously in one single dose." Initial intravenous doses, preceded "by one or more subcutaneous doses should not be greater than 0.25 milliliter." Subsequent doses are increased by similar amounts. This may be built up daily until 5 milliliters are administered. A marked reaction to either route indicates that the next dose should be decreased. Subsequently, it again may be increased cautiously.

3. *Analysis*—a. *Effectiveness.* There is no information relating to the effectiveness of the product.

b. *Safety.* No information on animal safety was provided by the manufacturer.

No information on human safety was provided by the manufacturer.

c. *Benefit-risk ratio.* The benefit-risk ratio for this product is low.

4. *Conclusions.* It is recommended that the product be placed in Category IIIB, and the appropriate license(s) be revoked for the following reasons:

a. There is no substantial evidence of safety or effectiveness.

b. There is no evidence presumptive of safety.

BACTERIAL ANTIGEN MADE FROM HEMOLYTIC AND NONHEMOLYTIC STREPTOCOCCI (STREPTOCOCCUS IMMUNOGEN, ARTHRITIS (BIO 327)) MANUFACTURED BY PARKE, DAVIS AND CO.

1. *Description.* This product consists of substances, i.e., antigens, extracted from the surfaces of bacterial cells by agitation in isotonic sodium chloride solution followed by centrifugation. The bacteria used include three beta hemolytic strains (Group A, no type, T-type 3/13 and Group B, Type 3), five alpha hemolytic (Group D, *S. sanguis* and 3 of *S. mitis*), and one gamma hemolytic *S. facalis.* The vaccine is standardized so that 1 milliliter contains antigens from approximately 2 billion bacterial cells. Purified cresol 0.2 percent is added as a preservative.

2. *Labeling.* The basis for the use of this agent dates to the period when streptococci were considered to be the cause of rheumatoid arthritis (Ref. 1).

Despite years of intensive search, no microorganism has been isolated which can be causally related to rheumatoid arthritis (Ref. 2). The ubiquitous presence of streptococci coupled with scattered reports of their isolation from blood cultures, the relative ease in demonstrating humoral antibodies to them, and the accepted association of Lancefield Group A streptococci with acute rheumatic fever is used as a rationale by some practitioners for the continued use of streptococcal vaccine in the treatment of rheumatoid arthritis.

The manufacturer's indications for the use of streptococcus immunogen, as a desensitizing agent, is stated to be "as an adjuvant to other established antiarthritic therapy." This indication is accompanied by a statement that "there is no uniform agreement concerning the effectiveness of this product." Cited contraindications for use include pregnancy, rheumatic fever, glomerulonephritis and patients receiving corticosteroid or other immunosuppressive therapy. A warning that the possibility exists that use of this product may induce streptococcal-associated disease states or exacerbate existing conditions is included.

3. *Analysis.* The nature of the antigenic material, or evidence that antigens actually exist in the product is not documented. The usual means for obtaining cell wall antigens (Ref. 3) are not used in the above-stated method.

The likelihood of significant or demonstrable representations of cell wall or surface antigens existing in such products, following what in essence is a vigorous saline wash, is exceedingly small. The fact that no washing of the harvested cells prior to the "saline extraction" is described, suggests that the product may contain significant amounts of calf serum agar as a contaminant and possible safety hazard.

Claims of effectiveness, as previously noted, are not uniformly accepted. Evidence of effectiveness is submitted either as uncontrolled or partially controlled studies or testimonial letters from individual physicians. The most detailed of these reports was submitted by Dr. I. Anderson and includes 15 cases (5 of which were supplied by a colleague) of which 7 had a condition described as "infectious sacroiliac arthritis." Total improvement was noted in 12 of 15 patients after 4 intravenous doses (initial dose of 0.2 milliliter with each of the following doses increased by 0.1 milliliter at 5-day intervals), and in the remaining 3 patients after 6 treatments. No controls were included. Safety data are limited to results of the general safety tests, marketing information and physician testimonials, including a statement from Dr. J. W. Townsend who reports on treating large numbers of patients per week.

The submitted medical literature includes a paper by Wetherby describing the intravenous use of streptococcal vaccines (not this manufacturer's product) in the treatment of chronic arthritis (Ref. 4). (See review of V-677 in this report which also discusses the Wetherby Study.) While this paper is of some interest, the product under review, streptococcus immunogen, was not used by Wetherby in his studies. As noted above, although the product is prepared by "saline agitation" of growth from strains of alpha, beta and gamma hemolytic streptococci, there is no documentation that streptococcal antigens are contained in the product as described.

The basis for utilization of the saline bacterial wash rests with a paper submitted by the manufacturer by Ferry and Fisher (Ref. 5) in which a variety of methods was employed in the extraction of so-called "ecto-antigens." Streptococcal antigens are purportedly demonstrated by the immunization of rabbits and the subsequent determination of agglutination and complement fixation titers, implying antibody-antigen reactions. The lack of controls, i.e., checks of the hyperimmune sera against agar products and serum absorption to remove nonspecific antibody, makes specificity difficult to evaluate and at best, only suggestive.

The demonstration of mouse protective soluble antigen of pneumococcus by Ferry and Fisher cannot be applied to the streptococci used in this preparation since no specific soluble substance exists for the involved streptococci. Ferry's report (Ref. 7) of the agar washings of a strain of beta hemolytic streptococcus (*Streptococcus scarlatiniae*) producing reactions identical to those induced by scarlet fever toxin (Dick toxin) a known extracellular product, suggests that the antigenic activity described by these authors may be of extracellular origin.

The remainder of the papers submitted include references to the nature of rheumatic and collagen diseases, the use of bacterial vaccines in asthma, the common cold and the use of bacterial acellular antigens in similar conditions. While these studies are of interest, none can be utilized to assess the effectiveness, safety, or the nature of the Parke-Davis product under review.

Contraindications for the use of vaccines containing Lancefield Group A streptococci in acute rheumatic fever and acute glomerulonephritis are indicated by reports describing cross-reacting antigens between streptococci and human heart muscle (Refs. 8 and 9), skin (Ref. 10) and kidney (Ref. 11) capable of inducing pathologic changes. Thus the safety of such agents is suspect. Despite the fact that deaths have not been directly related to streptococcal vaccines, the occurrence of renal involvement among the so-called "rheumatic diseases" coupled with the failure to monitor organ pathology in early studies raises serious questions concerning an "iceberg" effect for undetected vaccine toxicity.

The early hypotheses and observations relative to the causal relationship of alpha hemolytic streptococci to rheumatoid arthritis are speculative at best. For example, the demonstration that the blood of normal individuals is readily invaded by these organisms following oral manipulation (Ref. 12) explains (1) the early reports of their isolation from the blood of patients with a variety of disorders and (2) misinterpretations of their significance.

Although the concept of an infectious etiology for rheumatoid arthritis (Ref. 13) has not been totally discarded, the causal relationship of the streptococcus to this disorder has not been considered viable since the late 1930's. While no relationship ever has been established between these organisms and other forms of arthritis, the accepted role of Group A streptococci in acute rheumatic fever and acute glomerulonephritis has been considered a contraindication for the use of such vaccines in these diseases. The search for an immunologic relationship between these organisms and these "immune diseases" continues and remains an investigational and intellectual challenge (Ref. 14).

The continued use of this product in which the presumed streptococcal surface antigens have not been demonstrated (were they present they would create potential tissue and organ damage in humans) (Refs. 8 through 11) must be seriously questioned. That a number of practitioners and patients have employed them during their many years of existence, as attested by testimonial letters, in no way circumvents the lack of evidence for safety and effectiveness in the submission.

The inclusion of the Wetherby study (Ref. 4) with another streptococcal vaccine also is not valid evidence for the safety and effectiveness of the product under review in the treatment of arthritis.

4. *Conclusions.* It is recommended that this product be placed in Category II and that the appropriate license(s) be revoked because there are compelling reasons to assume a lack of safety and an unsatisfactory benefit-risk ratio for this product. In keeping with the Panel's statement regarding the use of Group A streptococcal strains and their derivatives, this product is considered hazardous.

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PIROMEN (PSEUDOMONAS POLYSACCHARIDE) MANUFACTURED BY TRAVENOL LABORATORIES, INC.

It has been known since the mid-eighteenth century that the inoculation of a wide variety of substances can induce "toxic" manifestations, including fever, in man and lower animals (Ref. 1 below). Many of these effects were seen during severe infections with gram-negative bacteria; the active factors were extracted from bacterial cells and nonviable, protein-free preparations. These were termed "endotoxins," and an extensive research effort on their mode of action and biochemical composition has continued to this day. While the main pharmacologic actions are present in all endotoxin preparations, variations result from the type of bacteria used and their method of extraction. Thus the extensive body of data on endotoxins can yield useful inferences, but cannot be precisely applied to effectiveness and safety considerations of PIROMEN.

Much of the initial impetus for endotoxin study and development was based on the presumed clinical usefulness of fever induction in diseases such as neurosyphilis. The basis for the alleged benefit of fever has never been understood, and its use has diminished steadily as other treatments have become available (penicillin for neurosyphilis, etc.). In a sense it belongs in the same category as a number of other procedures whose apparent value has been diminished and replaced by more uniformly effective procedures with less dangerous side effects. At the same time that fever therapy was decreasing, possible stimulating effects of endotoxins on the pituitary-adrenal axis were noted which in turn encouraged their continued use by some in a variety of allergic conditions but primarily as an adjuvant to other forms of therapy.

PIROMEN was developed in response to these needs in the early 1950's. It was initially prepared by Baxter Laboratories under the trade name "PYROMEN"; subsequently, the product and license were assumed by Travenol Laboratories, a subsidiary of Baxter, under the current name "PIROMEN."

1. *Description.* The pseudomonas species used was obtained from the American Type Culture Collection (No. 9229). Although not explained by the manufacturer, one investigative group states that pseudomonas was selected because it was not thought to be commonly pathogenic and could be cultured easily (Ref. 2). Preparation follows the procedure of Nesset et al. (Ref. 3). Bacteria are grown for 8 to 10 days, autoclaved, and trypsin added in a 1:50 enzyme substrate ratio. The digest is then dialyzed, centrifuged, and the supernatant lyophilized to a concentrate with a minimal pyrogenic dose of 0.3 microgram/kilogram in rabbits. Analysis reveals primarily polysaccharide with hexosamine as the only reducing sugar. A small amount of contaminating nucleic acid is present; no protein is detectable.

The preparation is buffered with M/6 sodium lactate to a pH of 6.8 and contains thimerosal 1:10,000 as a preservative. It is standardized by the dry weight of the concentrate and supplied in 10 ml. vials containing 4 mcg/ml. and 10 mcg/ml., and in 2 ml. vials containing 50 mcg/ml.

2. *Labeling*—a. *Package insert.* Pharmacologic activity is described as mediated primarily, but not exclusively, through the pituitary-adrenal system. Animal studies indicating activation of the reticuloendothelial system, temperature elevation and improvement in vascularity to traumatized areas are mentioned.

Indications are listed as adjuvant in nature for a variety of allergic and dermatologic conditions. It is specifically stated that PIROMEN has "proved of value" in perennial respiratory allergy, hay fever, allergic rhinitis, bronchial asthma, urticaria with angioedema, food allergy, and "fatigue syndrome of allergic origin." For dermatologic conditions, PIROMEN is said to have been "used successfully" in atopic dermatitis, infectious eczematoid dermatitis, urticaria with angioneurotic edema, contact dermatitis, otitis externa, vesicular eruptions, tinea and neurodermatitis.

Precautions listed are: Situations where the effects of temperature elevation may be deleterious to the patients (not specified in the insert); and it is stated that

> The drug should be administered with care in patients with a previous history of asthma because it may, on rare occasions, produce an asthmatic attack.

It is further mentioned that an attack has been reported in an indivdual with no previous history of asthma but that resumption of PIROMEN has not produced a recurrence. No reference source for this is presented. Standard current precautions on instrument sterility are also recommended.

Side effects are presented as "few and relatively minor", and it is stated that aspirin can relieve much of the discomfort. The sense of euphoria often associated with PIROMEN is mentioned.

Administration is recommended to be any parenteral route, although the intravenous is described as producing the most rapid effects. Because of variations in response threshold, initial doses of 1 or 2 micrograms intravenously are recommended with subsequent doses being increased by 1 microgram per injection until a clinical response is obtained. If a fever is produced, it is suggested that the next dose be reduced by ½ to 1 microgram. Levels of maintenance dosage or length of time treatment should be continued is not clearly specified—the statement is made that—

> Dosage should be maintained at the level which produces the greatest clinical response.

A general program of three injections the first week followed by weekly inoculations for "as long as necessary" is suggested. It is noted that some cases may require two or more injections weekly to obtain the most beneficial responses.

Also included is a description of how the product is supplied and a reference list of 36 pertinent published articles.

b. *Other descriptive material.* The package itself contains no therapeutic claims, and PIROMEN has not been advertised. The only other promotional material presented are drug index cards, which contain essentially the same material as described in the package insert.

3. *Analysis*—a. *Theoretical considerations*—(1) *Effectiveness.* A vast literature on the mode of action and effects of bacterial endotoxins has accumulated during the past 20 years. The diversity of effects appears almost endless, and it is not surprising that a theoretical basis for possible effectiveness in human disease states can be found. With respect to infectious diseases, for example, it has been noted that endotoxins have important effects upon blood granulocytes, the reticuloendothelial system, antibody production, complement, lysozyme, interferon, vascular reactivity, production and dissipation of heat, metabolism, and other systems that can influence resistance to infection specifically or nonspecifically (Ref. 4). Certainly, the possibility of human therapeutic usefulness could be logically considered.

The current manufacturer's suggested therapeutic usefulness of PIROMEN is primarily for certain allergic disorders, on the rationale that endotoxins stimulate the release of pituitary and adrenocortical hormones. This concept was not initially readily accepted (Ref. 1). Subsequent studies have clearly shown increased blood levels of these hormones following PIROMEN inoculation in humans (Refs. 5 through 9). In fact, the drug is now used as a diagnostic aid in

the assessment of pituitary reserve.

In these publications it should be noted that there has been a consistent finding that laboratory indications of increased hormonal activity occurred only when fever was also induced. If the specific hormonal effects are accepted as the rationale for therapeutic use, this would suggest that subpyrexial doses of PIROMEN would be ineffective. It has been suggested that a virtue of PIROMEN is that it may in effect substitute for steroid therapy, causing fewer undesirable side effects and less rebound phenomena. Again, if therapeutic effects are to be ascribed to hormonal action, it is difficult to see why the indirect stimulation by an endotoxin would be easier to control than direct administration of known amounts of adrenocortical hormones.

The use of endotoxins as nonspecific pyrogenic agents has previously been mentioned. In some instances, the alleged beneficial effects may have been mediated through the pituitary-adrenal axis as described above. Many other effects of fever may have been important in therapy, but this field remains in a somewhat confused state and the possible benefit of PIROMEN as a nonspecific pyrogen cannot be said to rest on any firm theoretical foundation.

(2) *Potency standards.* A variety of methods has been used for extraction of endotoxin from bacteria and it appears to be generally agreed that a lipopolysaccharide fraction possesses much of the activity. Precise relationships have still not been worked out and it has been stated,

> This is not to say that the essential activities of endotoxins do not reside in a phosphorylated lipopolysaccharide; however, to date no complete proof exists that a specific basis constituent is essential for any of the toxic or other biological activities common to the endotoxin macro-molecule (Ref. 10).

Thus a standard based on precise chemical composition is not available. Bioassays have therefore been used, the most thoroughly studied being fever production in rabbits. Perhaps the limulus amebocyte lysate test would also be useful for standardizing this product but the degree of specificity of this test has been questioned (Refs. 45 through 47).

The standardization of PIROMEN is based on dry weight but rabbit pyrogenic assays are routinely performed as a potency check of each lot. Since the mode of action of PIROMEN has not been precisely defined, an entirely logical potency standard is not available. The methods used, i.e., standardization by dry weight with a potency check by bioassay of fever in rabbits, seem to be in accord with the current state of knowledge.

(3) *Safety.* As with effectiveness considerations, the published list of dangerous effects of endotoxins in animals is so extensive and variable that any number of theoretical dangers in human use can be devised. These include shock, thrombocytopenia, tissue necrosis, generalized Schwartzman reaction, antiphagocytic action, renal cortical necrosis and adrenal necrosis (Ref. 1). Evaluation must be tempered by the realization that the data are based on endotoxins from a variety of bacterial sources, widely divergent methods of extraction, and products of varying degrees of purity. Also, most are strongly dose-dependent with animal data indicating an extensive range between minimal doses required for pyrogenic effects and amounts shown to produce dangerous reactions.

It has been stated on the manufacturer's drug index card and frequently in the literature (Refs. 15 through 18) that PIROMEN is non-anaphylactogenic. While classical anaphylactic responses are rarely seen in animals following PIROMEN administration, the specific research efforts to produce such responses have been few. Extensive work with other endotoxin preparations have shown varying degrees of antigen activities of even highly purified lipopolysaccharides. In fact, the question is often raised as to the role of hypersensitivity reactions to endotoxin in the genesis of the biological effects (Ref. 11). Thus, this theoretical danger should not be lightly dismissed. A more specific related example is the Schwartzman reaction, frequently demonstrable in laboratory animals following endotoxin usage. The mechanism is still not completely understood, but its appearance is related closely to such factors as the route of administration and the exact timing of inoculation. The clinical use of PIROMEN in humans follows no set pattern of route or timing. It thus is possible that certain combinations could lead to dangerous immunological reactions in man.

Considerable evidence exists that there is a relationship between lesions produced by endotoxin and the circulating levels of alpha adrenergic amines (levarterenol and epinephrine). The pathogenic potential of endotoxin is enhanced by higher blood levels of these amines (Ref. 12). These effects of endotoxin bring into serious question the recommendation (package insert) for the use of epinephrine to treat high-dose PIROMEN-induced asthma.

Finally, it should be noted that susceptibility to endotoxin in laboratory animals can vary with genetic type and that certain disease states in humans, such as liver disease, can increase susceptibility to effects of endotoxin, and that fever induction in man by any mechanism always has been associated with dangerous reactions (Refs. 1, 13, and 14).

b. *Available data*—(1) *Effectiveness.* Twenty-six published studies were identified by the Panel as dealing with the effectiveness of PIROMEN in human disease states. A summary of these is presented in tabular form in a supplement to the Panel report (Ref. 50). Excluded are individual case reports and those dealing with the use of PIROMEN as a test of pituitary and bone marrow reserve.

Of these studies, the vast majority are uncontrolled compilations of treated cases, performed between 1949 and 1955. The majority of the uncontrolled studies indicate some possible degree of effectiveness but valid interpretation is limited not only by the lack of placebo controls, but also by the lack of precise methods of evaluation, considerable variations in dosage, route, and scheduling of inoculations, lack of consistent definition of cases, and insufficient numbers in many of the disease categories.

The report of Guy and Green (Ref. 19) employed saline placebo controls. Judged by present-day standards, the study was flawed in respect to its randomization procedure, inadequacy of the crossover technique, type and timing of followup, and method of statistical analysis. It also should be noted that currently acceptable modes of therapy were not used in either control or experimental groups. Nonetheless, a real attempt at a blind study was made, and the results were suggestive of effectiveness with respect to chronic recurrent atopic eczema: of 15 patients treated with placebo, 2 improved, 8 showed no change and 5 became worse. Of 28 patients treated with PIROMEN, 17 improved, 7 showed no change and 4 became worse.

Samter and Kofoed (Ref. 31) also conducted a double-blind controlled trial but recipients in this case were patients with rhinitis, bronchial asthma and urticaria. Of 19 patients treated with subcutaneous (SC) PIROMEN, 8 improved, 7 showed no change and 4 became worse. Of 19 placebo patients, 6 improved, 9 showed no change and 4 became worse. The authors concluded that the clinical effectiveness of the product was not superior to a placebo containing its diluent M/6 molar sodium lactate.

The article by Welsh and Ede (Ref. 16) describes the results in 1,037 subcutaneously treated cases of various dermatoses and compares them with patients on therapeutic regimens without PIROMEN. The effects are quite impressive numerically with respect to infectious eczematoid dermatitis, atopic dermatitis, urticaria, angioneurotic edema and contact dermatitis. Little benefit was noted in a variety of other inflammatory, infectious and miscellaneous skin conditions. Unfortunately, it is impossible to determine from the article what the controls were, how they were selected, or how they were evaluated.

The vast majority of disease conditions studied are all subject to spontaneous variations and also exemplify the "well known tendency of allergic patients to respond favorably but temporarily to any new and dramatic treatment" (Ref. 22). Thus, the uncontrolled studies, despite their number, provide little if any basis for the scientific evaluation of effectiveness. Negative results, however, may have some inferential value. Besides the negative double-blind study (Ref. 31), asthma in general, fared less well than allergic dermatoses in the uncontrolled studies. In the one instance in which systematic measures of respiratory capacity were made, no significant responses to PIROMEN were uncovered (Ref. 28).

One interesting possible use of PIROMEN is in familial cold urticaria, a relatively rare condition with an autosomal dominant inheritance pattern. The prior

administration of PIROMEN in relatively large intravenous amounts (38 and 25 micrograms) in two patients prevented the development of urticaria after subsequent exposure to cold (Ref. 48). The mechanism for this action is unknown.

Since effectiveness could not be regularly demonstrated, it follows that no logical route and dosage of PIROMEN can be established. It is interesting that investigators are almost evenly divided on the question of whether a dosage sufficient to produce fever is necessary for therapeutic action. In only rare instances was temperature actually measured, the criteria most often employed being chills and/or subjective feelings of warmth. Since PIROMEN is now recommended as "adjunct" therapy, it is important to recognize that the studies referred to were conducted 17 to 25 years ago. Many did not use steroids for routine therapy, while others used forms of steroid therapy which were not as effective as they are currently. Thus the alleged effectiveness of PIROMEN in comparison to standard forms of therapy might well be less today.

A large section of the manufacturer's presentation is devoted to the use of PIROMEN in the assessment of bone marrow and pituitary reserve. There are adequate data to support this (Refs. 5 through 9, 42 and 43), but it should be clearly noted that these are diagnostic procedures performed on an experimental basis.

It also appears that PIROMEN is not used alone, but rather as part of a battery of tests, no single one of which is taken as a sole, valid indicator.

A variety of laboratory animal data are available on possible beneficial actions of PIROMEN such as wound healing and nervous system regeneration. While such data stimulated early human trials on multiple sclerosis (Ref. 37) and duodenal ulcer (Ref. 38), current indications for PIROMEN usage are primarily allergic and dermatologic and have no direct relationship to model systems in lower animals.

(2) *Safety.* A summary of human trials and possible adverse effects is presented in tabular form in a supplement to the Panel report (Ref. 50), including studies from the effectiveness summary plus pituitary assessment and individual case report data. As indicated, over 2,000 persons are reported in the literature to have received PIROMEN inoculations. A considerable variation in reported adverse or side effects from study-to-study can be noted. Analysis is made difficult because many of the studies do not specify precise details of dosage, timing, or route of administration, nor how adverse effects were sought.

Three deaths were temporally associated with PIROMEN administration. The case reported by Walton and Elliot (Ref. 35) occurred in a young woman with a previous history of severe asthma, psychologic instability and aspirin sensitivity. Her fourth hospital admission was characterized by less severe asthma, and she was started on a course of intravenous PYROMEN. Following her last (7th) dose she developed a severe attack, required epinephrine and aminophylline, and died suddenly 1 hour and 25 minutes following the intravenous PYROMEN. The case reported by Wittich (Ref. 32) was an adult male with a longstanding history of severe asthma. He had been hospitalized in status asthmaticus, was nonresponsive to ACTH and cortisone, and a course of PIROMEN therapy was initiated. He became worse after three or four inoculations, and expired 2 days later. The report by Lonsen and Liebert (Ref. 34) was that of a 52-year-old general paretic who was suffering from cord bladder. "Very shortly" after the first intravenous PIROMEN injection the patient developed a high temperature that persisted, the nonprotein nitrogen rose markedly, and the patient expired 10 days later. Other deaths have been reported during the course of PIROMEN therapy, but these occurred in severely ill patients with malignant hypertension and bore no patterns of timing or associated symptoms which could be related to PIROMEN (Refs. 40 and 41).

A pattern suggestive of asthma hyperreactivity can be noted. One death was seen, and in one instance an asthma attack occurred in a person with no prior asthma history (Ref. 24).

A number of precipitations of asthmatic attacks in prior asthmatics were seen (Refs. 21 through 23, 25, and 32). On the basis of available descriptions these were not severe and were easily controlled. The one study employing ventilatory tests showed no change following PIROMEN (Ref. 28).

Two studies (Refs. 24 and 26) noted possible bleeding tendencies as incidental observations. Extensive laboratory determinations, including bleeding and clotting times, platelet and reticulocyte counts, and vitamin C, calcium and phosphorus levels were performed; while all were within normal limits, no specific studies, both before and after PIROMEN inoculation, were performed, thus no slight to moderate effects could be determined (Ref. 24).

The two patients reported with shock-like effects had been on PIROMEN for several months without reactions. A single intravenous dose of 4 micrograms was followed in a few minutes by faintness, pallor, tachycardia, sweating, nausea, abdominal pain and "other signs of shock." Each recovered without supportive treatment and received no subsequent PIROMEN therapy. This prompted the authors to state that,

> PIROMEN is said to be nonanaphylactogenic, but these two cases suggest caution in its use after an interval from previous treatment (Ref. 22).

Other reactions noted included development of ectopic beats in those with previous myocardial damage (Ref. 32), symptoms suggestive of possible avitaminosis B and C in four patients, and mental disturbances in previously depressed patients (Ref. 24).

The most common effects were "constitutional reactions" of fever, headache, malaise, chills, muscle aches and nausea. These were mostly mild and transient, only on rare occasion causing sufficient discomfort to induce lack of cooperation from the patient. These effects were seen almost exclusively after intravenous administration of PIROMEN. It was specifically noted by several investigators that no correlation could be found between dosage level and likelihood of reaction. Reaction has been noted after as little as 0.5 microgram and not seen after doses as high as 50 micrograms. No systematic evidence is available as to whether reactions consistently occur in the same persons.

Areas of deficiency in human safety data include:

(i) Systematic long-term evaluation. Most studies are short-term, and whatever laboratory data are available have been collected after the initial inoculation.

(ii) Relatively few attempts to investigate alteration of immunologic response in humans. In one study no dermal hypersensitivity could be found after repeated PIROMEN inoculations, and there was no influence on ragweed sensitivity (Ref. 31), the only specific attempt.

(iii) Lack of controlled studies. It should be realized that controlled studies are necessary not only for effectiveness determinations, but also to accurately assess induced complications as indicated in the general findings.

Extensive animal studies have been conducted with this product. Additional animal studies can be found in the literature; these studies are consistent with the articles presented. In particular, detailed pathologic studies have been performed (Ref. 44).

Studies in a variety of animals show that relatively high doses are needed for obvious danger signs to appear. Relatively few studies of long-term, repetitive doses have been performed, and relatively few have been specifically designed to search for abnormal immunologic reactions, although failure to induce anaphylaxis in guinea pigs has been specifically noted (Ref. 31).

The manufacturer's presentation states that the LD–50 of PIROMEN in laboratory animals is in the area of 70,000 micrograms/kilogram, whereas the highest dosage reported as having been given to humans is 50 micrograms total dose. This should be tempered by the realization that the LD–50 is the dose at which one-half of the animals die, hardly an endpoint useful for clinical considerations. The dose-response curve is characteristically S-shaped, thus the dose that would kill 1 of 1,000 animals cannot be extrapolated. Furthermore, human sensitivity to endotoxin is higher than that of many animals. Thus the ratio between toxic and therapeutic effects may be less than generally supposed.

c. *Labeling.* On the basis of the preceding discussion, it is clear that the pack-

age insert and drug index cards contain several statements which are misleading and not in accord with the weight of scientific evidence.

d. *Benefit-to-risk considerations.* Precise risk rates for PIROMEN cannot be determined because of the lack of systematic reporting and controlled trial methodology. It is recognized that the association of adverse clinical symptoms with drug administration does not imply a cause and effect relationship. In the case of PIROMEN it can be noted that the deaths occurred in those with preexisting illnesses whose deaths may have had only a coincidental relationship to PIROMEN administration. Risk determinations in the case of PIROMEN are therefore largely judgmental, based on indirect features of timing, biological plausibility, and consistency of relationship. "Substantial" direct evidence of either safety or the lack of it cannot be found.

With these considerable limitations in mind, the Panel considers that:

(1) Risk definitely outweighs benefit in the condition of bronchial asthma since an association of adverse effects to PIROMEN has been found without concomitant benefit.

(2) Risk-to-benefit ratios in the conditions generally categorized as "atopic dermatitis" are indeterminate. Neither component can be accurately weighed. Considerations are:

(i) Effectiveness data are not consistent. While data of studies suggest a measurable degree of effectiveness, advocacy of PIROMEN as "adjunct" therapy based on treatment schedules of many years ago gives rise to questions of its current usefulness. No indication is present that the use of PIROMEN has significant (or any) modern day support from the medical practice or scientific communities;

(ii) Calculation of risk required a denominator of total persons receiving the product, available in the case of PIROMEN, only by tabulating numbers inoculated from a variety of published literature reports. This amounts to somewhat more than 2,000 recipients, of which approximately one-half received the inoculation intravenously. Even in the absence of any reported ill effects, on a statistical basis a mortality rate of 1:1,000 following intravenous inoculation cannot be excluded. Of the deaths reported, one could be plausibly considered to have a possible causal relationship to the administration of PIROMEN. While no such causal relationship can be proven, it further indicates that the possibility of mortality rates of 1:1,000 cannot be ignored.

(3) Risk outweighs benefits in all other conditions of possible therapeutic use since no evidence of benefit is present.

(4) Risk-to-benefit ratio in the instances of the use of PIROMEN as a diagnostic test for pituitary or bone marrow reserve is difficult to assess, since it is not a commonly used procedure and outcome is so heavily weighed by the underlying disease condition. There are, however, certain situations where the information obtained may be pertinent to the management of the condition.

4. *Conclusions*—a. *Critique.* Federal regulations have clearly specified the responsibility of the manufacturer in the presentation of information to the Food and Drug Administration: to provide all information, favorable and unfavorable, pertinent to an evaluation of the safety, effectiveness and labeling of his product. In this light it is interesting to examine the Panel tabulation appearing as a supplement to the report (Ref. 50), which summarizes the literature review in respect to whether the articles have been specifically included in the manufacturer's presentation or not. With respect to the second category (those articles included as references in the package insert), it should be explained that the lack of effectiveness or possible adverse reactions were not themselves mentioned in the insert, rather, the article title was given. Thus a physician would have to actually review each one to learn of the adverse effects or lack of effectiveness noted in these reports. One exception is the mention in the package insert of asthma induction in a person without a previous history of asthma attacks. In this instance the specific reference is not presented.

The third category (those literature references not presented as direct enclosures or referred to in the package insert), was found after a completely routine library search. No specific modern computer aids were used in the search. References to these articles could also be found in the bibliographies attached to submitted review articles. Thus in a purely technical sense all information could have been obtained from the manufacturer's presentation.

A clear progression is noted, with the literature presented by the manufacturer showing favorable results while those not referenced showing less impressive effectiveness data and suggestions of danger. It is noteworthy that one of the double-blind controlled studies (Ref. 31) which indicated lack of effectiveness of PIROMEN and is not referred to, has a footnote stating that the work was financially supported by the manufacturer. Presumably, Travenol Laboratories might have had reason to become aware of the data.

The manufacturer's presentation does not include any information on sales volume or any other measure to indicate how extensive the use of PIROMEN is. This lack of information has important bearings on both safety and effectiveness considerations since:

(1) It is impossible to evaluate even crudely the absence of reported adverse effects in recent years, i.e., 1960 to present. Conceivably this could mean that very little PIROMEN has been used.

(2) The diseases for which PIROMEN is advocated have not significantly decreased over time; if the drug is in fact useful, one would expect some evidence for continued widespread prescribing by practicing physicians.

Since no pertinent survey data were submitted, no conclusive answers are available. A useful indirect measure, however, is the extent to which PIROMEN is advocated in standard medical textbooks. The following is a survey of randomly selected material from a university medical library:

(i) PIROMEN is not mentioned or referenced as a possible therapeutic agent in:

"Andrew's Diseases of the Skin," 1971; Goodman and Gilman, "The Pharmacological Basis of Therapeutics," 1970; "Merck Manual," 12th Ed., 1971; Fitzpatrick et al., "Dermatology in General Medicine," Current Therapy, 1973; Criep, L., editor, "Dermatologic Allergy: Immunology, Diagnosis, Management," 1967; Sherman, W., editor, "Hypersensitivity: Mechanisms and Management," 1968; Swineford, O., editor, "Asthma and Hay Fever," 1971.

(ii) PIROMEN is mentioned directly or indirectly in three publications:

"Medical Letter," Vol. 11, 1969. Although PIROMEN, typhoid vaccine, and other fever-inducing agents stimulate ACTH secretion, they are less effective than ACTH or corticosteroids in the treatment of allergic disorders. Most "Medical Letter" consultants believe that PIROMEN has no place in contemporary therapeutics.

Kendig, E. L., editor, "Disorders of the Respiratory Tract in Children," 1969. Sometimes respiratory bacterial vaccines and extracts are also used for nonspecific protein effect, as were typhoid and pertussis vaccines, sterile milk, snake venom and autohemotherapy injections some years ago. The efficacy of these agents has never been conclusively proved by controlled studies. The same is true for injections of precipitated sulfur extracts of *Rhus quercifolia* (Anergex), bacterial pyrogens (PIROMEN) and ethylene disulfonate.

Sheldon, Lovell and Mathews, "A Manual of Clinical Allergy," 1967. Typhoid vaccine and other foreign proteins probably stimulated the pituitary adrenal axis and have been largely supplanted by treatment with the corticosteroids themselves.

b. *Recommendations.* It is recommended that this product be placed in Category IIIB and that the appropriate license(s) be revoked for the following reasons:

(1) There is no substantial evidence of safety or effectiveness.

(2) There is no evidence presumptive of safety.

(3) If PIROMEN is to be used to evaluate the adrenal-pituitary axis or bone marrow reserve, these new functions require evaluation as a new biological.

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Conclusions and Recommendations Submitted by the Panel to the Commissioner

On the basis of data in the manufacturers' submissions and extensive survey of the medical literature, the Panel concludes that safety, according to current criteria, has not been demonstrated for any product reviewed. However, the Panel finds that for the six products classified by the Panel as Category IIIA products, there is reasonable inference of safety to permit continued licensure while further studies concerning safety and effectiveness are conducted and evaluated. The following conclusions and recommendations are applicable to the six products:

1. *Inadequate data to determine safety and efficacy.* a. Certain bacteria and their derivatives which normally inhabit the respiratory tract were thought to cause secondary bacterial infections during acute respiratory disease and primary respiratory disease or "bacterial allergy." Other bacteria, cultured from specific lesions, such as abscesses, were thought to cause this problem. These factors often were the only reason for selecting the bacteria and their derivatives to produce "bacterial vaccines and bacterial antigens with no U.S. standard of potency."

b. Safety and effectiveness of the products rest largely upon information, in the form of anecdotes and results of informal studies, which were collected during the long years of use of the products.

c. For some products, identification and quantitation of the components in the final product are lacking.

d. Evidence of lot-to-lot comparability (either by composition or function) for each product is incomplete or absent.

e. The indications for uses of the products are not clearly defined. Routes of administration and dosages (especially for children) are not based upon recognizable criteria. Generally, dosage is determined by trial and error. In addition,

toxic reactions are often attributed to overdosage.

Accordingly, the Panel recommends that additional data be obtained from controlled studies conducted, as recommended by the Panel, in parallel with continued use of the product.

They recommended the following testing schedule:

(1) The manufacturer should be granted 6 months in which to file with FDA, a notice of intent to undertake studies designed to identify the components in the final product(s). Such studies should be completed in a period not to exceed 1 year from the date of filing with FDA the notice of intent to undertake the required studies.

(2) An additional like time period (1 year) shall be allowed for the quantification of the components in the final product(s).

(3) If the manufacturer fails to comply with this schedule, the product(s) shall be removed from the market.

(4) Within 1 year after the components in the final product(s) have been identified and quantified, the manufacturer shall design and submit to FDA, for acceptance, a protocol for a clinical study.

(5) The proposed conduct of the clinical study shall be in conformity with existing regulations and the recommendations of the Panel.

(6) A final report of the clinical study shall be completed within 3 years of the date of acceptance of the protocol by FDA.

(7) Extension or abrogation of all of the cited time limits may be granted or withdrawn at the discretion of FDA.

2. *Streptococci.* The Panel concluded that Group A beta hemolytic streptococci, alone or in combination, in bacterial vaccines and bacterial antigens are unacceptably hazardous.

Accordingly, they recommend that Group A streptococci and its derivatives be removed from licensed products.

3. *Bacteriophage.* The Panel is concerned about the possible adverse effects of long-term parenterally administered bacteriophage, live or killed.

Accordingly, they recommend that phages be identified and removed in the initial steps of the manufacturing process of licensed products, insofar as it is technically feasible.

4. *Labeling.* Labeling of products was found to be uniformly deficient and unacceptable.

Accordingly, the Panel recommends that labeling be modified to conform to current FDA requirements and include a patient information insert.

THE COMMISSIONER'S RESPONSE TO THE PANEL'S RECOMMENDATIONS

The Commissioner is responding to the Panel's recommendations as follows:

1. The Panel recognized that a number of their recommendations for further studies may be beyond the capability of some of the manufacturers involved. Consequently they recommended that the Federal Government undertake and sponsor some of the required studies.

The Commissioner acknowledges the potential benefit to the public health from additional studies regarding bacterial vaccines and antigens. As noted by the Panel, the Commissioner anticipated that it may be desirable for the Federal Government to sponsor such studies as so provided in § 601.25(h)(1).

The Commissioner hereby solicits comments on the expenditure of Federal funds for the study of these products. These studies would be designed to determine if any products reviewed by the Panel are effective for unidentified segments of the population, a hypothesis suggested by some of the anecdotal information available to the Panel. When the final order is published, the Commissioner will notify appropriate agencies so that such studies may be considered and priorities assigned.

2. The Commissioner notes the Panel's views of the eventual need to replace thimerosal as a preservative in biological products. This problem is of major concern primarily with skin test products which are inoculated intradermally and where thimerosal-induced positive skin reactions may interfere with an accurate diagnostic reading. However, there is no evidence that thimerosal affects either the safety or the effectiveness of bacterial or viral vaccines. These products are generally inoculated subcutaneously and reactions have presented little if any problem. The Commissioner recognizes that there are only a few preservatives that have been found to be safe and effective for use in injectable biological products. Other substances, frequently employed as preservatives in nonbiological products, are unacceptable because of interactions with the proteinaceous components of biologicals and because they may also be sensitizing. Due to these problems, extensive research is required to demonstrate the propriety of the new preservative in each biological product. Therefore, when other preservatives are shown to be safe and effective in ongoing studies of biological products, regulations proposing their use in place of thimerosal will be considered.

3. The Panel recommended that a study designed to establish guidelines for chronic toxicity testing in animals be undertaken.

The Commissioner recognizes this problem. In the FEDERAL REGISTER of July 15, 1977 (42 FR 36490) and November 19, 1976, (41 FR 51206), the Commissioner proposed new rules governing periodic reporting of data on animal toxicity testing on IND drugs and good laboratory practices, respectively. Issues relating to long-term testing in animals will be the subject of further study both within the agency and in various outside scientific forums as the opportunity becomes available.

4. The Panel recommended that Group A streptococcus and its derivatives be removed from all bacterial vaccines and antigens.

The Commissioner agrees with the Panel's conclusion that Group A streptococcal antigens in bacterial vaccines and antigens may induce dangerous tissue reactions in humans. Accordingly, the Commissioner proposes to amend the biologics regulations by adding a new § 610.19 *Status of specific products; Group A streptococcus* to prohibit Group A streptococcus organisms or their derivatives from these biological products.

5. The Panel opposed the future use of any bacterial vaccine and bacterial antigen having "No U.S. Standard of Potency." They recommended that standards of potency be developed, within a reasonable period, for all bacterial products permitted to remain in interstate commerce.

The Commissioner agrees with the Panel's conclusion. All such products have now been reviewed by the Panel. Once the Panel report is implemented, there will be no licensed bacterial vaccine or bacterial antigen for which potency standards have not been established.

6. The Panel recommended that, insofar as it is technically possible, bacteriophages be identified and removed in the initial manufacturing process of bacterial vaccines and bacterial antigens.

The Commissioner notes the Panel's concerns regarding the possible adverse effects to patients receiving bacterial vaccines and bacterial antigens containing bacteriophages. He also notes and concurs that this risk, if any, is theoretical and therefore difficult to define. There is no evidence that adverse reactions related to the presence of bacteriophages have occurred in any of hundreds of millions of persons who have received biologic products containing bacteriophages. In addition, man has an enormous environmental contact with bacteriophages. The human intestinal tract harbors bacteriophages and under certain conditions, bacteriophages may be present in human blood and tissues. In earlier decades of this century massive doses of bacteriophages have been purposely administered to humans in an attempt to treat bacterial diseases, and more recently bacteriophages have been given experimentally in the diagnosis of immunologic disorders. In no instance has there been evidence that administration of bacteriophages to man or animals has been harmful. It is also recognized that the detection and removal of bacteriophages from these products is subject to great technical difficulty and may, for some organisms, be impossible. Notwithstanding these considerations, the Commissioner will encourage research efforts to detect, identify, and, wherever feasible, to remove bacteriophages from the products. Bacteriophages that are not removed must be demonstrated to be safe and, if intentionally included, effective.

7. The Panel recommended that bacterial vaccines and bacterial antigens with "No U.S. Standard of Potency,"

which consist of individually licensed organisms, or their derivatives or mixtures of organisms or their derivatives, be grouped into regulatory categories, as follows:

a. *Category I—Biological products determined to be safe and effective and not misbranded and should continue in interstate commerce.* None of the products reviewed were placed into this category. The Commissioner agrees with the Panel's findings and recommendations and hereby proposes to adopt its conclusion. Comments and/or additional data on this classification are invited.

b. *Category II—Biological products determined to be unsafe or ineffective or to be misbranded and should not continue in interstate commerce.* Bacterial Vaccine Diagnostics manufactured by Hollister-Stier, Division of Cutter Laboratories, license No. 8; Bacterial Vaccine T-50 Made From Streptococcus Pyogenes Type L-8 or by prescription, manufactured by Hollister-Stier, Division of Cutter Laboratories, license No. 8; and Bacterial Antigen Made From Hemolytic and Nonhemolytic Streptococci (Streptococcus Immunogen, arthritis (Bio. 327)) manufactured by Parke, Davis and Company, license No. 1. As previously stated, Group A Streptococcus organisms and their derivatives, when included in any other mixed vaccine product, have been found to be unsafe.

The Commissioner agrees with the Panel's findings and recommendations concerning these drugs and, in accordance with §§ 601.5 and 601.25(f)(2), intends to publish a notice of opportunity for hearing to revoke the licenses for these products by or before (*insert date 30 days after date of publication*). Interested persons may comment and/or submit additional data in response to the notice.

c. *Category IIIA—Biological products for which available data are insufficient to classify their safety and effectiveness but which may remain in interstate commerce pending completion of testing.* Respiratory UBA (UBA-32) manufactured by Eli Lilly and Co., license No. 56; Respiratory B.A.C. manufactured by Hoffmann Laboratories, Inc., license No. 283; Staphylococcal B.A.C. manufactured by Hoffman Laboratories, Inc., license No. 283: Bacterial Vaccines Mixed Respiratory (MRV or MRVI) manufactured by Hollister-Stier, Division of Cutter Laboratories, license No. 8; Bacterial Vaccines for Treatment, Special Mixtures containing only the following organisms—*Staphylococcus* (*aureus* and *albus*), *Streptococcus* (viridans and nonhemolytic) *Diplococcus pneumoniae, Neisseria catarrhalis, Klebsiella pneumoniae, Haemophilus influenzae* manufactured by Hollister-Stier, Division of Cutter Laboratories, license No. 8; Staphylococcus Toxoid Sclavo manufactured by Istituto Sieroterapico Vaccinogeno Toscano "Sclavo," license No. 238; Staphylococcus Toxoid; Formalinized: Dilution No. 1, Dilution No. 2; and Digest-Modified manufactured by Lederle Laboratories Division, license No. 17.

The Commissioner agrees with the Panel's findings and recommendations concerning these drugs and, in accordance with § 601.25(f)(3), hereby proposes that products listed in Category IIIA remain on the market and their licenses remain in effect on an interim basis: *Provided*, That (1) Group A streptococcal organisms and their derivatives, where present, are removed (and license applications amended accordingly) and (2) satisfactory potency standards are developed and acceptable data based on scientifically sound studies (as recommended in the Panel Report) be submitted to demonstrate efficacy in humans. Such studies shall be in accordance with the Panel's recommendations, as amended below, and § 601.25(h). Failure to submit adequate data, in the form of a license amendment, within the specified time will result in the publication of a notice of an opportunity to revoke the product license.

The Commissioner agrees with the Panel's recommendations for the time for completion of the studies, except that portion of the recommendation granting 6 months following publication of the final order for filing a notice of intent to undertake studies adequate and appropriate to resolve the questions raised about the product. The Commissioner concludes that with the carefully developed schedule for studies developed by the Panel, 6 months is unnecessary for the sole purpose of indicating intent regarding the undertaking of necessary studies. Section 601.25(h)(1) prescribes 30 days for this step and the Commissioner sees no reason to change this prescribed time.

The Panel also recommended that protocols should include both short- and long-term surveillance of recipients of these products. On July 26, 1977, Commissioner Kennedy appeared before the Subcommittee on Health and Scientific Research of the Senate Committee on Human Resources to testify in support of Senate Bill 1831, which would give FDA increased authority over the development of drugs, including postmarket testing and surveillance. The Commissioner concurs with the Panel's recommendation, but is not now proposing an overall plan for followup surveillance of the reviewed products. This matter may be reconsidered as particular protocols are submitted and evaluated.

Since the Panel's conclusions concerning the effectiveness of Category IIIA drugs are a material fact within the meaning of 21 U.S.C. 321(n) and 21 CFR 1.21 and the failure to disclose the conclusions causes these drugs to be misbranded, the Commissioner also proposes that (1) the circular and the promotional material for these drugs must have a prominent boxed statement referencing the need for further data to fully establish effectiveness; (2) a written informed consent be obtained from participants in the requisite additional studies, an explanation of the product and the purpose of the study is given and a clear opportunity to refuse to participate in the study is presented; and (3) a patient information insert be included with all Category IIIA products continued in interstate commerce.

In the FEDERAL REGISTER of September 30, 1977, the Commissioner proposed revision of 21 CFR 601.25(h) to require items (1) and (2) above for all Category IIIA biologicals. The Commissioner proposes in this document to further amend 21 CFR 601.25(h) to require a patient insert for all Category IIIA bacterial vaccines and bacterial antigens that have been designated as having "No. U.S. Standard of Potency." The basis for requiring patient labeling in certain circumstances is set forth in the FEDERAL REGISTER of April 7, 1975 (40 FR 15392) concerning prescription drugs. (See also 21 CFR 310.501.)

d. *Category IIIB—Biological products for which available data are insufficient to classify their safety and effectiveness and should not continue in interstate commerce.* Mixed Respiratory Bacteria, manufactured by Center Laboratories, Inc., license No. 193; Staphage Lysate (SPL), Type I and Types I and III for Staphylococcal Disease, manufactured by Delmont Laboratories, Inc., license No. 299; Bacterial Vaccine Made From Pneumococci, Streptococci, *H. influenzae, and N. Catarrhalis* (ENTORAL), manufactured by Eli Lilly and Co., license No. 56; Mixed Vaccine No. 4 with *H. influenzae* (V-306), manufactured by Eli Lilly and Co.; license No. 56; Combined Vaccine No. 4 with Catarrhalis (V-151), manufactured by Eli Lilly and Co.; license No. 56; Staphylococcus Vaccine (V-563), manufactured by Eli Lilly and Co., license No. 56; V-677 Streptococcus Vaccines (Intravenous) manufactured by Eli Lilly and Co., license No. 56; Staphylococcus-Streptococcus UBA (UBA-48) (Undenatured Bacterial Antigen), manufactured by Eli Lilly and Co., license No. 56; Bacterial Vaccine Made From Typhoid H Antigen (V-763 Typhoid H Antigen), manufactured by Eli Lilly and Co., license No. 56; Respiratory Bacterial Antigen Complexes (B.A.C.) (Pooled Stock B.A.C. #1, manufactured by Hoffmann Laboratories, Inc., license No. 283; Pooled Stock B.A.C. #2, manufactured by Hoffmann Laboratories, Inc., license No. 283; Gram Negative B.A.C., manufactured by Hoffmann Laboratories, Inc, license No. 283); Pooled Skin B.A.C., manufactured by Hoffmann Labortaories, Inc., license No. 283; Bacterial Vaccines for Treatment, Special Mixtures containing one or more of the following organisms, *A. aerogenes, C. pseudodiphtheriticum, C. corynebacterium* (*Propionibacterium*) *acnes, C. xerosis, E. coli, G. tetragena, H. pertussis* (not reviewed by the panel), *P. vulgaris, P. aeruginosa, S. enteritidis, S. paradysenteriae* (Type Y), *S. paratyphi, S. schottmuelleri, S. typhosa, S. dysenteriae* (not reviewed by the panel) *S. flexneri, S. jacalis, Staphylococcus albus,* and *Staphylococcus aureus,* manufactured by Hollister-Stier, Division of Cutter Laboratories, license No. 8; Immunovac Respiratory Vaccine (Bio. 616), manufactured by Parke, Davis and Co., license No. 1; *N. Catarrhalis* immunogen (Combined) (Bio. 340), manufactured by Park,

Davis and Co., license No. 1; *N. catarrhalis* Vaccine (Combined) (Bio. 615), manufactured by Parke, Davis and Co., license No. 1; Mixed Infection Phylacogen (Bio. 596), manufactured by Parke, Davis and Co., license No. 1; Immunovac Oral Vaccine Tablets (Bio. 2155), manufactured by Parke, Davis and Co., license No. 1; PIROMEN (Pseudomonas polysaccharide), manufactured by Travenol Laboratories, Inc., license No. 140.

The Commissioner agrees with the Panel's findings and recommendations concerning these drugs and, in accordance with §§ 601.5 and 601.25(f)(3), intends to publish a notice of an opportunity for hearing to revoke the licenses for these products by or before (*insert 30 days after date of publication*). Interested persons may comment and/or submit additional data in response to the notice. These revocation proceedings will be unnecessary for Bacterial Vaccine Made from Pneumococci, Streptococci, *H. influenzae*, and *N. catarrhalis* (ENTORAL) (V-404, V-408); Mixed Vaccine No. 4 with *H. influenzae* (V-306); Combined Vaccine No. 4 with Catarrhalis (V-151); Staphylococcus Vaccine (V-563); Staphylococcus-Streptococcus UBA (UBA-48) (Undenatured Bacterial Antigen); Bacterial Vaccine Made from Typhoid H Antigen (V-763 Typhoid H Antigen) because, at the request of Eli Lilly and Co., the licenses were revoked on April 11, 1977.

8. The Commissioner intends to change the form of licenses for bacterial vaccines involved in this review to cover final products rather than organisms. In the past, licenses for these products were issued for specific organisms which were used for the manufacture of one or more final products. For many years, however, licenses for all other biological products have been issued for final products based on a determination that the product, as well as its component parts, have the requisite quality. To make licensure of bacterial products uniform with licenses for all other biological products, manufacturers of products in Category IIIA are advised to request that the Director, Bureau of Biologics, issue licenses for their final products, in place of licenses now held for the organisms.

The Commissioner has carefully considered the environmental effects of the proposed regulation and, because the proposed action will not significantly affect the quality of the human environment, has concluded that an environmental impact statement is not required. A copy of the environmental impact assessment is on file with the Hearing Clerk, Food and Drug Administration.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201, 502, 505, 701, 52 Stat. 1040–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 352, 355, 371)), the Public Health Service Act (sec. 351, 58 Stat. 702 as amended (42 U.S.C. 262)), and the Administrative Procedure Act (secs. 4, 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 702, 703, 704)), and under authority delegated to him (21 CFR 5.1), the Commissioner is proposing that Parts 601, and 610 in Subchapter F of Chapter I of Title 21 of the Code of Federal Regulations be amended as follows:

1. In Part 601, § 601.25 is amended by adding new paragraph (h)(6) to read as follows:

§ 601.25 Review procedures to determine that licensed biological products are safe, effective, and not misbranded under prescribed, recommended, or suggested conditions of use.

* * * * * *

(h) * * *

(6) Bacterial Vaccines and Bacterial Antigens in Category IIIA which have been designated as having "No U.S. Standard of Potency" shall contain a printed patient insert, in lay language, prominently incorporating the information on safety and effectiveness substantially as provided to the prescribing physician in the labeling approved in the license application, including the status of these drugs consistent with the boxed statement required by paragraph (h)(4) of this section.

2. In part 610, § 610.19 is added to Subpart B, to read as follows:

§ 610.19 Status of specific products; Group A streptococcus.

The presence of Group A streptococcal organisms and their derivatives in bacterial vaccines and bacterial antigens may induce dangerous tissue reactions in humans. Available data demonstrate that they are unsafe as ingredients in these products. Group A streptococcal organisms and their derivatives are prohibited from bacterial vaccines and bacterial antigens. Any bacterial vaccine or bacterial antigen containing Group A streptococcal organisms or their derivatives in interstate commerce is in violation of section 351 of the Public Health Service Act (42 U.S.C. 262).

Interested persons may, on or before January 9, 1978, submit to the Hearing Clerk (HFC–20), Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20857, written comments regarding this proposal. Four copies of all comments shall be submitted, except that individuals may submit single copies of comments, and shall be identified with the Hearing Clerk docket number found in brackets in the heading of this document. Received comments may be seen in the above office between the hours of 9 a.m. and 4 p.m., Monday through Friday.

NOTE.—The Food and Drug Administration has determined that this document does not contain a major proposal requiring preparation of an inflation impact statement under Executive Order 11821 and OMB Circular A–107. A copy of the inflation impact assessment is on file with the Hearing Clerk, Food and Drug Administration.

Dated: September 22, 1977.

DONALD KENNEDY,
Commissioner of Food and Drugs.

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